TITLE OF THE INVENTION
CGRP RECEPTOR ANTAGONISTS

BACKGROUND OF THE INVENTION

CGRP (Calcitonin Gene-Related Peptide) is a naturally occurring 37-amino acid peptide that is generated by tissue-specific alternate processing of calcitonin messenger RNA and is widely distributed in the central and peripheral nervous system. CGRP is localized predominantly in sensory afferent and central neurons and mediates several biological actions, including vasodilation. CGRP is expressed in alpha- and beta-forms that vary by one and three amino acids in the rat and human, respectively. CGRP-alpha and CGRP-beta display similar biological properties. When released from the cell, CGRP initiates its biological responses by binding to specific cell surface receptors that are predominantly coupled to the activation of adenylyl cyclase. CGRP receptors have been identified and pharmacologically evaluated in several tissues and cells, including those of brain, cardiovascular, endothelial, and smooth muscle origin.

CGRP is a potent vasodilator that has been implicated in the pathology of cerebrovascular disorders such as migraine and cluster headache. In clinical studies, elevated levels of CGRP in the jugular vein were found to occur during migraine attacks (Goadsby et al., Ann. Neurol., 1990, 28, 183-187). CGRP activates receptors on the smooth muscle of intracranial vessels, leading to increased vasodilation, which is thought to be the major source of headache pain during migraine attacks (Lance, Headache Pathogenesis: Monoamines, Neuropeptides, Purines and Nitric Oxide, Lippincott-Raven Publishers, 1997, 3-9). The middle meningeal artery, the principle artery in the dura mater, is innervated by sensory fibers from the trigeminal ganglion which contain several neuropeptides, including CGRP. Trigeminal ganglion stimulation in the cat resulted in increased levels of CGRP, and in humans, activation of the trigeminal system caused facial flushing and increased levels of CGRP in the external jugular vein (Goadsby et al., Ann. Neurol., 1988, 23, 193-196). Electrical stimulation of the dura mater in rats increased the diameter of the middle meningeal artery, an effect that was blocked by prior administration of CGRP(8-37), a peptide CGRP antagonist (Williamson et al., Cephalalgia, 1997, 17, 525-531). Trigeminal ganglion stimulation increased facial blood flow in the rat, which was inhibited by CGRP(8-37) (Escott et al., Brain Res. 1995, 669, 93-99). Electrical stimulation of the trigeminal ganglion in marmoset produced an increase in facial blood flow that could be blocked by the non-peptide CGRP antagonist BIBN4096BS (Doods et al., Br. J. Pharmacol.,

2000, 129, 420-423). Thus the vascular effects of CGRP may be attenuated, prevented or reversed by a CGRP antagonist.

CGRP-mediated vasodilation of rat middle meningeal artery was shown to sensitize neurons of the trigeminal nucleus caudalis (Williamson et al., The CGRP Family: Calcitonin Gene-Related Peptide (CGRP), Amylin, and Adrenomedullin, Landes Bioscience, 2000, 245-247). Similarly, distention of dural blood vessels during migraine headache may sensitize trigeminal neurons. Some of the associated symptoms of migraine, including extra-cranial pain and facial allodynia, may be the result of sensitized trigeminal neurons (Burstein et al., Ann. Neurol. 2000, 47, 614-624). A CGRP antagonist may be beneficial in attenuating, preventing or reversing the effects of neuronal sensitization.

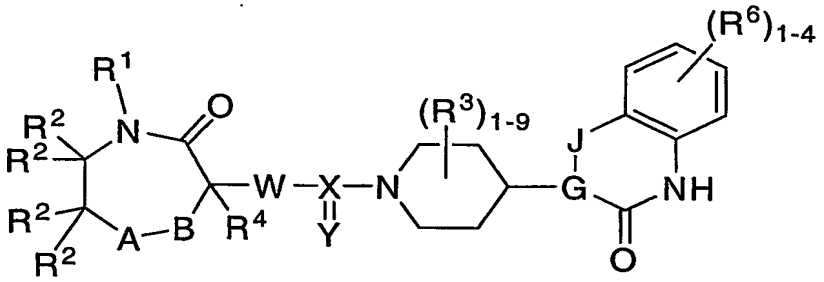
The ability of the compounds of the present invention to act as CGRP antagonists makes them useful pharmacological agents for disorders that involve CGRP in humans and animals, but particularly in humans. Such disorders include migraine and cluster headache (Doods, Curr Opin Inves Drugs, 2001, 2 (9), 1261-1268; Edvinsson et al., Cephalalgia, 1994, 14, 320-327); chronic tension type headache (Ashina et al., Neurology, 2000, 14, 1335-1340); pain (Yu et al., Eur. J. Pharm., 1998, 347, 275-282); chronic pain (Hulsebosch et al., Pain, 2000, 86, 163-175); neurogenic inflammation and inflammatory pain (Holzer, Neurosci., 1988, 24, 739-768; Delay-Goyet et al., Acta Physiol. Scanda. 1992, 146, 537-538; Salmon et al., Nature Neurosci., 2001, 4(4), 357-358); eye pain (May et al. Cephalalgia, 2002, 22, 195-196), tooth pain (Awawdeh et al., Int. Endocrin. J., 2002, 35, 30-36), non-insulin dependent diabetes mellitus (Molina et al., Diabetes, 1990, 39, 260-265); vascular disorders; inflammation (Zhang et al., Pain, 2001, 89, 265), arthritis, bronchial hyperreactivity, asthma, (Foster et al., Ann. NY Acad. Sci., 1992, 657, 397-404; Schini et al., Am. J. Physiol., 1994, 267, H2483-H2490; Zheng et al., J. Virol., 1993, 67, 5786-5791); shock, sepsis (Beer et al., Crit. Care Med., 2002, 30 (8), 1794-1798); opiate withdrawal syndrome (Salmon et al., Nature Neurosci., 2001, 4(4), 357-358) morphine tolerance (Menard et al., J. Neurosci., 1996, 16 (7), 2342-2351); hot flashes in men and women (Chen et al., Lancet, 1993, 342, 49; Spetz et al., J. Urology, 2001, 166, 1720-1723); allergic dermatitis (Wallengren, Contact Dermatitis, 2000, 43 (3), 137-143); psoriasis; encephalitis, brain trauma, ischaemia, stroke, epilepsy, and neurodegenerative diseases (Rohrenbeck et al., Neurobiol. of Disease 1999, 6, 15-34); skin diseases (Geppetti and Holzer, Eds., Neurogenic Inflammation, 1996, CRC Press, Boca Raton, FL), neurogenic cutaneous redness, skin rosaceousness and erythema; tinnitus (Herzog et al., J. Membrane Biology, 2002, 189(3), 225); inflammatory bowel disease, irritable bowel syndrome, (Hoffman et al. Scandinavian Journal of Gastroenterology, 2002, 37(4) 414-422) and cystitis. Of particular

importance is the acute or prophylactic treatment of headache, including migraine and cluster headache.

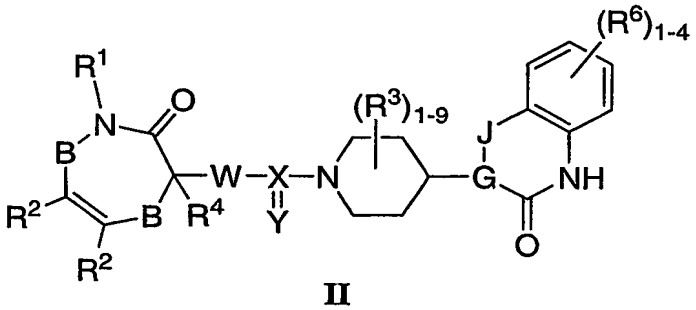
The present invention relates to compounds that are useful as ligands for CGRP receptors, in particular antagonists for CGRP receptors, processes for their preparation, their use in therapy, pharmaceutical compositions comprising them and methods of therapy using them.

SUMMARY OF THE INVENTION

The present invention is directed to compounds of Formula I and Formula II:



I

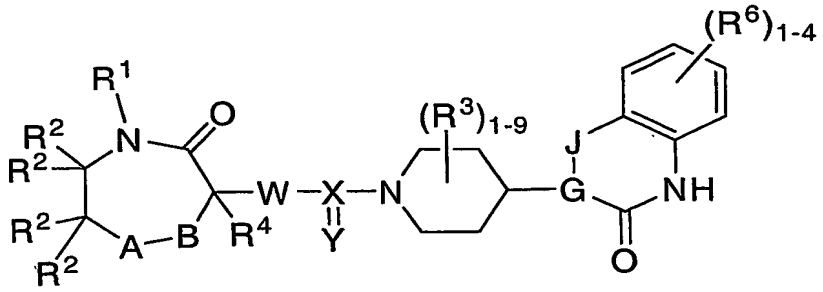


II

(where variables R^1, R^2, R^3, R^4, R^6, A, B, G, J, W, X and Y are as defined herein) useful as antagonists of CGRP receptors and useful in the treatment or prevention of diseases in which the CGRP is involved, such as headache, migraine and cluster headache. The invention is also directed to pharmaceutical compositions comprising these compounds and the use of these compounds and compositions in the prevention or treatment of such diseases in which CGRP is involved.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to CGRP antagonists which include compounds of the formula I:



I

wherein:

A is a bond, $C(R^2)_2$, O, $S(O)_m$ or NR^2;

B is $(C(R^2)_2)_n$;

R^1 is selected from:

1) H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_{3-6} cycloalkyl, and heterocycle, unsubstituted or substituted with one or more substituents independently selected from:

a) C_{1-6} alkyl,

b) C_{3-6} cycloalkyl,

c) aryl, unsubstituted or substituted with 1-5 substituents where the substituents are independently selected from R^4,

d) heteroaryl, unsubstituted or substituted with 1-5 substituents where the substituents are independently selected from R^4,

e) heterocycle, unsubstituted or substituted with 1-5 substituents where the substituents are independently selected from R^4,

f) $(F)_pC_{1-3}$ alkyl,

g) halogen,

h) OR^4,

i) $O(CH_2)_s OR^4$,

j) CO_2R^4,

k) $(CO)NR^{10}R^{11}$,

l) $O(CO)NR^{10}R^{11}$,

m) $N(R^4)(CO)NR^{10}R^{11}$,

n) $N(R^{10})(CO)R^{11}$,

o) $N(R^{10})(CO)OR^{11}$,

p) $SO_2NR^{10}R^{11}$,

q) $N(R^{10})\ SO_2R^{11}$,

r) $S(O)_mR^{10}$,

s) CN,

t) $NR^{10}R^{11}$,

u) $N(R^{10})(CO)NR^4R^{11}$, and,

v) $O(CO)R^4$,

2) aryl or heteroaryl, unsubstituted or substituted with one or more substituents independently selected from:

a) C_{1-6} alkyl,

b) C_{3-6} cycloalkyl,

c) aryl, unsubstituted or substituted with 1-5 substituents where the substituents are independently selected from R^4,

d) heteroaryl, unsubstituted or substituted with 1-5 substituents where the substituents are independently selected from R^4,

e) heterocycle, unsubstituted or substituted with 1-5 substituents where the substituents are independently selected from R^4,

f) $(F)_pC_{1-3}$ alkyl,

g) halogen,

h) OR^4,

i) $O(CH2)_sOR^4$,

j) CO_2R^4,
k) $(CO)NR^{10}R^{11}$,
l) $O(CO)NR^{10}R^{11}$,
m) $N(R^4)(CO)NR^{10}R^{11}$,
n) $N(R^{10})(CO)R^{11}$,
o) $N(R^{10})(CO)OR^{11}$,
p) $SO_2NR^{10}R^{11}$,
q) $N(R^{10})\ SO_2R^{11}$,
r) $S(O)_mR^{10}$,
s) CN,
t) $NR^{10}R^{11}$,
u) $N(R^{10})(CO)NR^4R^{11}$, and
v) $O(CO)R^4$;

R^2 is independently selected from:

1) H, C_0-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_{3-6} cycloalkyl and heterocycle, unsubstituted or substituted with one or more substituents independently selected from:
a) C_{1-6} alkyl,
b) C_{3-6} cycloalkyl,
c) aryl, unsubstituted or substituted with 1-5 substituents where the substituents are independently selected from R^4,
d) heteroaryl, unsubstituted or substituted with 1-5 substituents where the substituents are independently selected from R^4,
e) heterocycle, unsubstituted or substituted with 1-5 substituents where the substituents are independently selected from R^4, f) $(F)_pC_{1-3}$ alkyl,
g) halogen,
h) OR^4,
i) $O(CH_2)_sOR^4$,
j) CO_2R^4,
k) $(CO)NR^{10}R^{11}$,
l) $O(CO)NR^{10}R^{11}$,

m) $N(R^4)(CO)NR^{10}R^{11}$,
n) $N(R^{10})(CO)R^{11}$,
o) $N(R^{10})(CO)OR^{11}$,
p) $SO_2NR^{10}R^{11}$,
q) $N(R^{10})\ SO_2R^{11}$,
r) $S(O)_mR^{10}$,
s) CN,
t) $NR^{10}R^{11}$,
u) $N(R^{10})(CO)NR^4R^{11}$, and,
v) $O(CO)R^4$,

2) aryl or heteroaryl, unsubstituted or substituted with one or more substituents independently selected from:
a) $C_{1\text{-}6}$ alkyl,
b) $C_{3\text{-}6}$ cycloalkyl,
c) aryl, unsubstituted or substituted with 1-5 substituents where the substituents are independently selected from R^4,
d) heteroaryl, unsubstituted or substituted with 1-5 substituents where the substituents are independently selected from R^4,
e) heterocycle, unsubstituted or substituted with 1-5 substituents where the substituents are independently selected from R^4,
f) $(F)_pC_{1\text{-}3}$ alkyl,
g) halogen,
h) OR^4,
i) $O(CH_2)_sOR^4$,
j) CO_2R^4,
k) $(CO)NR^{10}R^{11}$,
l) $O(CO)NR^{10}R^{11}$,
m) $N(R^4)(CO)NR^{10}R^{11}$,
n) $N(R^{10})(CO)R^{11}$,
o) $N(R^{10})(CO)OR^{11}$,
p) $SO_2NR^{10}R^{11}$,
q) $N(R^{10})\ SO_2R^{11}$,
r) $S(O)_mR^{10}$,

s) CN,
t) $NR^{10}R^{11}$,
u) $N(R^{10})(CO)NR^4R^{11}$, and
v) $O(CO)R^4$,

or, any two independent R^2 on the same or adjacent atoms may be joined together to form a ring selected from cyclobutyl, cyclopentenyl, cyclopentyl, cyclohexenyl, cyclohexyl, phenyl, naphthyl, thienyl, thiazolyl, thiazolinyl, oxazolyl, oxazolinyl, imidazolyl, imidazolinyl, imidazolidinyl, pyridyl, pyrimidyl, pyrazinyl, pyrrolyl, pyrrolinyl, morpholinyl, thiomorpholine, thiomorpholine S-oxide, thiomorpholine S-dioxide, azetidinyl, pyrrolidinyl, piperidinyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydropyridyl, furanyl, dihydrofuranyl, dihydropyranyl and piperazinyl;

R^{10} and R^{11} are independently selected from: H, C_{1-6} alkyl, $(F)_pC_{1-6}$ alkyl, C_{3-6} cycloalkyl, aryl, heteroaryl, and benzyl, unsubstituted or substituted with halogen, hydroxy or C_1-C_6 alkoxy, where R^{10} and R^{11} may be joined together to form a ring selected from: azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl, which is unsubstituted or substituted with 1-5 substituents where the substituents are independently selected from R^4;

R^4 is independently selected from: H, C_{1-6} alkyl, $(F)_pC_{1-6}$ alkyl, C_{3-6} cycloalkyl, aryl, heteroaryl and benzyl, unsubstituted or substituted with halogen, hydroxy or C_1-C_6 alkoxy;

W is O, NR^4 or $C(R^4)_2$;

X is C or S;

Y is O, $(R^4)_2$, NCN, NSO_2CH_3, $NCONH_2$, or Y is O_2 when X is S;

R^6 is independently selected from H and:

a) C_{1-6} alkyl,
b) C_{3-6} cycloalkyl,
c) aryl, unsubstituted or substituted with 1-5 substituents where the substituents are independently selected from R^4,

d) heteroaryl, unsubstituted or substituted with 1-5 substituents where the substituents are independently selected from R^4,

e) heterocycle, unsubstituted or substituted with 1-5 substituents where the substituents are independently selected from R^4,

f) $(F)_pC_{1-3}$ alkyl,

g) halogen,

h) OR^4,

i) $O(CH_2)_sOR^4$,

j) CO_2R^4,

k) $(CO)NR^{10}R^{11}$,

l) $O(CO)NR^{10}R^{11}$,

m) $N(R^4)(CO)NR^{10}R^{11}$,

n) $N(R^{10})(CO)R^{11}$,

o) $N(R^{10})(CO)OR^{11}$,

p) $SO_2NR^{10}R^{11}$,

q) $N(R^{10})\ SO_2R^{11}$,

r) $S(O)_mR^{10}$,

s) CN,

t) $NR^{10}R^{11}$,

u) $N(R^{10})(CO)NR^4R^{11}$, and

v) $O(CO)R^4$;

G-J is selected from: N, $N-C(R^5)_2$, $C=C(R^5)$, C=N; $C(R^5)$, $C(R^5)-C(R^5)_2$, $C(R^5)-C(R^5)_2-C(R^5)_2$, $C=C(R^5)-C(R^5)_2$, $C(R^5)-C(R^5)=C(R^5)$, $C(R^5)-C(R^5)_2-N(R^5)$, $C=C(R^5)-N(R^5)$, $C(R^5)-C(R^5)=N$, $C(R^5)-N(R^5)-C(R^5)_2$, $C=N-C(R^5)_2$, $C(R^5)-N=C(R^5)$, $C(R^5)-N(R^5)-N(R^5)$, $C=N-N(R^5)$, $N-C(R^5)_2-C(R^5)_2$, $N-C(R^5)=C(R^5)$, $N-C(R^5)_2-N(R^5)$, $N-C(R^5)=N$, $N-N(R^5)-C(R^5)_2$ and $N-N=C(R^5)$;

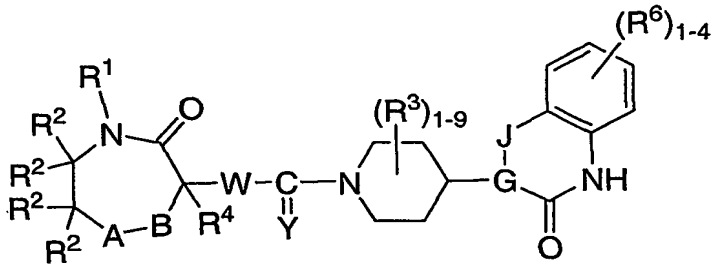
R^5 is independently selected from H, substituted or unsubstituted C_1-C_3 alkyl, OR^4, $N(R^4)_2$ and CO_2R^4;

R^3 is independently selected from H, substituted or unsubstituted C_1-C_3 alkyl, F, CN and CO_2R^4;

	p is	0 to 2q+1, for a substituent with q carbons;
	m is	0, 1 or 2;
	n is	0 or 1;
5	s is	1, 2 or 3;

and pharmaceutically acceptable salts and individual diastereomers thereof.

Further embodiments of the invention are CGRP antagonists of formula I which
10 include compounds of the formula Ia:



Ia

15 wherein:
A is a bond, $C(R^2)_2$, O, $S(O)_m$ or NR^2;
B is $(C(R^2)_2)_n$;
n is 0 or 1;
R^1, R^2, R^4, W, R^3, R^6, and G-J are as defined in formula I;
20 Y is O, $(R^4)_2$, NCN, NSO_2CH_3 or $NCONH_2$,
and pharmaceutically acceptable salts and individual stereoisomers thereof.

Still further embodiments of the invention are CGRP antagonists of formula I which include compounds of the formula Ib:

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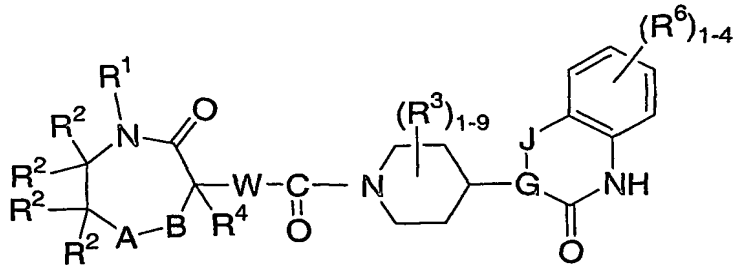


Ib

wherein:

A is a bond, $C(R^2)_2$, O, $S(O)_m$ or NR^2;

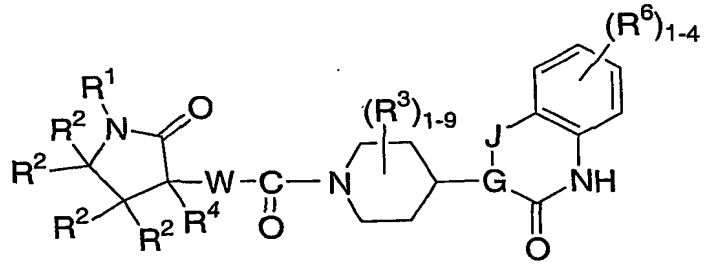
B is $(C(R^2)_2)_n$;

n is 0 or 1;

R^1, R^2, R^4, W, R^3, R^6, and G-J are as defined in formula I;

and pharmaceutically acceptable salts and individual stereoisomers thereof.

Additional embodiments of the invention are CGRP antagonists of formula I which include compounds of the formula Ic:



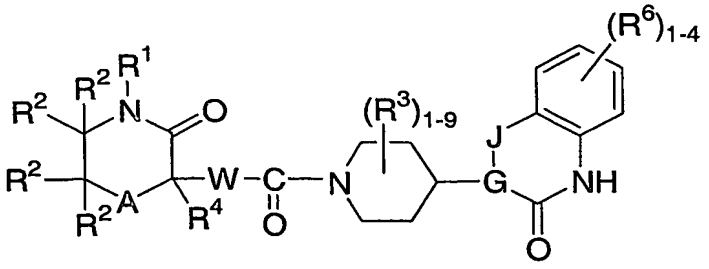
Ic

wherein:

R^1, R^2, R^4, W, R^3, R^6, and G-J are as defined in formula I;

and pharmaceutically acceptable salts and individual stereoisomers thereof.

Additional embodiments of the invention are CGRP antagonists of formula I which also include compounds of the formula Id:



Id

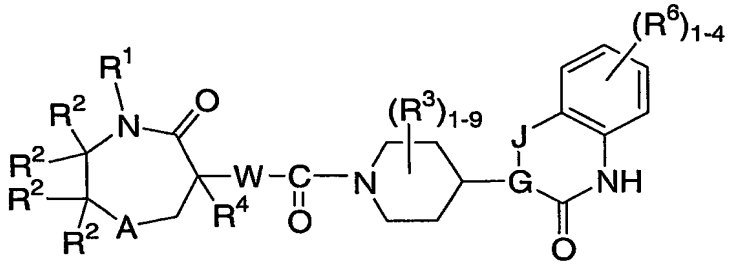
wherein:

A is $C(R^2)_2$, O, $S(O)_m$ or NR^2;

R^1, R^2, R^4, W, R^3, R^6 and G-J are as defined in formula I;

and pharmaceutically acceptable salts and individual stereoisomers thereof.

Additional embodiments of the invention are CGRP antagonists of formula I which include compounds of the formula Ie:



Ie

wherein:

A is $C(R^2)_2$, O, $S(O)_m$ or NR^2;

R^1, R^2, R^4, W, R^3, R^6, and G-J are defined in formula I;

and pharmaceutically acceptable salts and individual stereoisomers thereof.

Further embodiments of the invention are CGRP antagonists of formulae Ia –Ie, wherein:

R^1 is selected from:

1) H, C_1-C_6 alkyl, C_{3-6} cycloalkyl and heterocycle, unsubstituted or substituted with one or more substituents independently selected from:

a) C_{1-6} alkyl,
b) C_{3-6} cycloalkyl,
c) aryl, unsubstituted or substituted with 1-5 substituents where the substituents are independently selected from R^4,
d) heteroaryl, unsubstituted or substituted with 1-5 substituents where the substituents are independently selected from R^4,
e) heterocycle, unsubstituted or substituted with 1-5 substituents where the substituents are independently selected from R^4,
f) $(F)_pC_{1-3}$ alkyl,
g) halogen,
h) OR^4,
i) $O(CH_2)_sOR^4$,
j) CO_2R^4,
k) CN,
l) $NR^{10}R^{11}$, and
m) $O(CO)R^4$, and

2) aryl or heteroaryl, unsubstituted or substituted with one or more substituents independently selected from:
a) C_{1-6} alkyl,
b) C_{3-6} cycloalkyl,
c) $(F)_pC_{1-3}$ alkyl,
d) halogen,
e) OR^4,
f) CO_2R^4,
g) $(CO)NR^{10}R^{11}$,
h) $SO_2NR^{10}R^{11}$,
i) $N(R^{10})\ SO_2R^{11}$,
j) $S(O)_mR^4$,
k) CN,
l) $NR^{10}R^{11}$, and
m) $O(CO)R^4$;

R^2 is selected from:

1) H, C_0-C_6 alkyl, C_2-C_6 alkynyl, C_{3-6} cycloalkyl and heterocycle, unsubstituted or substituted with one or more substituents independently selected from:
   a) C_{1-6} alkyl,
   b) C_{3-6} cycloalkyl,
   c) aryl, unsubstituted or substituted with 1-5 sustituents where the substituents are independently selected from R^4,
   d) heteroaryl, unsubstituted or substituted with 1-5 substituents where the substituents are independently selected from R^4,
   e) heterocycle, unsubstituted or substituted with 1-5 substituents where the substituents are independently selected from R^4,
   f) $(F)_pC_{1-3}$ alkyl,
   g) halogen,
   h) OR^4,
   i) $O(CH_2)_sOR^4$,
   j) CO_2R^4,
   k) $S(O)_mR^4$,
   l) CN,
   m) $NR^{10}R^{11}$, and
   n) $O(CO)R^4$;

2) aryl or heteroaryl, unsubstituted or substituted with one more substituents independently selected from:
   a) C_{1-6} alkyl,
   b) C_{3-6} cycloalkyl,
   c) $(F)_pC_{1-3}$ alkyl,
   d) halogen,
   e) OR^4,
   f) CO_2R^4,
   g) $(CO)NR^{10}R^{11}$,
   h) $SO_2NR^{10}R^{11}$,
   i) $N(R^{10})\ SO_2R^{11}$,
   j) $S(O)_mR^4$,
   k) CN,
   l) $NR^{10}R^{11}$, and

m) $O(CO)R^4$,

or, any two independent R^2 on the same or adjacent atoms may be joined together to form a ring selected from cyclobutyl, cyclopentenyl, cyclopentyl, cyclohexenyl, cyclohexyl, phenyl, naphthyl, thienyl, thiazolyl, thiazolinyl, oxazolyl, oxazolinyl, imidazolyl, imidazolinyl, imidazolidinyl, pyridyl, pyrimidyl, pyrazinyl, pyrrolyl, pyrrolinyl, morpholinyl, thiomorpholine, thiomorpholine S-oxide, thiomorpholine S-dioxide, azetidinyl, pyrrolidinyl, piperidinyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydropyridyl, furanyl, dihydrofuranyl, dihydropyranyl and piperazinyl;

R^{10} and R^{11} are independently selected from: H, C_{1-6} alkyl, $(F)_pC_{1-6}$ alkyl, C_{3-6} cycloalkyl, aryl, heteroaryl and benzyl, unsubstituted or substituted with halogen, hydroxy or C_1-C_6 alkoxy, where R^{10} and R^{11} may be joined together to form a ring selected from: azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl and morpholinyl, which is unsubstituted or substituted with 1-5 substituents where the substituents are independently selected from R^4

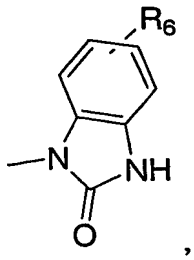
R^4 is independently selected from: H, C_{1-6} alkyl, $(F)_pC_{1-6}$ alkyl, C_{3-6} cycloalkyl, aryl, heteroaryl and benzyl, unsubstituted or substituted with halogen, hydroxy or C_1-C_6 alkoxy;

W is O, NR^4 or $C(R^4)_2$;

G-J is selected from:

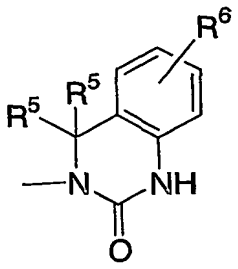
N, such that when G-J is so defined the following structure forms:

:



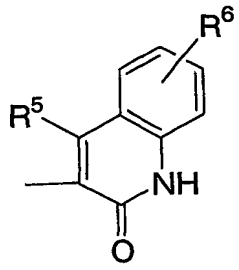
,

N–C(R^5)$_2$, such that when G-J is so defined the following structure forms:



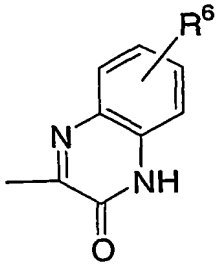
,

C=C(R^5), such that when G-J is so defined the following structure forms:



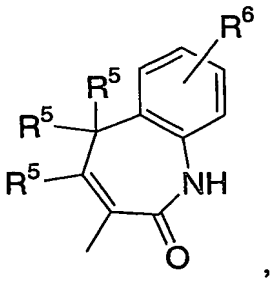
,

C=N, such that when G-J is so defined the following structure forms:



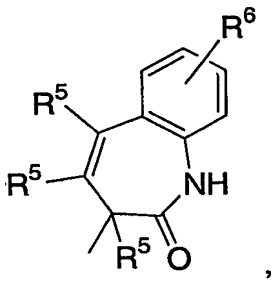
,

C=C(R^5)-C(R^5)$_2$, such that when G-J is so defined the following structure forms:



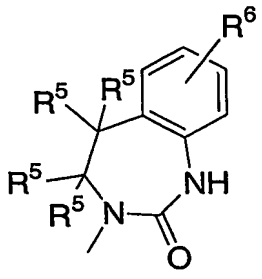
,

$C(R^5)$-$C(R^5)$=$C(R^5)$, such that when G-J is so defined the following structure forms:



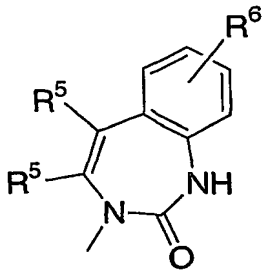
,

N-$C(R^5)_2$-$C(R^5)_2$, such that when G-J is so defined the following structure forms:



, and

N-$C(R^5)$=$C(R^5)$, such that when G-J is so defined the following structure forms:



;

R^6 is independently selected from H and:

a) C_{1-6} alkyl,
b) C_{3-6} cycloalkyl,
c) $(F)_pC_{1-3}$ alkyl,
d) halogen,
e) OR^4,
f) CO_2R^4,
g) $(CO)NR^{10}R^{11}$,
h) $SO_2NR^{10}R^{11}$,
i) $N(R^{10})\ SO_2R^{11}$,
j) $S(O)_mR^4$,
k) CN,
l) $NR^{10}R^{11}$, and
m) $O(CO)R^4$;

R^5 is independently selected from H, substituted or unsubstituted C_1-C_3 alkyl, CN, OR^4, $N(R^4)_2$ and CO_2R^4;

R^3 is independently selected from H, substituted or unsubstituted C_1-C_3 alkyl, F, CN and CO_2R^4;

p is 0 to 2q+1, for a substituent with q carbons
m is 0 to 2;
s is 1 to 3;
and pharmaceutically acceptable salts and individual stereoisomers thereof.

Still further embodiments of the invention are CGRP antagonists of formulae Ia – Ie, wherein:

R^1 is selected from:

1) H, C_1-C_6 alkyl, C_{3-6} cycloalkyl and heterocycle, unsubstituted or substituted with one or more substituents independently selected from:
   a) C_{1-6} alkyl,
   b) C_{3-6} cycloalkyl,
   c) phenyl, unsubstituted or substituted with 1-5 substituents where the substituents are independently selected from R^4,
   d) heteroaryl, unsubstituted or substituted with 1-5 substituents where the substituents are independently selected from R^4, and where heteroaryl is selected from:
      imidazole, isoxazole, oxazole, pyrazine, pyrazole, pyridazine, pyridine, pyrimidine, and thiazole;
   e) heterocycle, unsubstituted or substituted with 1-5 substituents where the substituents are independently selected from R^4, and where heterocycle is selected from:
      azetidine, dioxane, dioxolane, morpholine, oxetane, piperazine, piperidine, pyrrolidine, tetrahydrofuran, and tetrahydropyran;
   f) $(F)_pC_{1-3}$ alkyl,
   g) halogen,
   h) OR^4,
   i) $O(CH_2)_sOR^4$,
   j) CO_2R^4,
   k) CN,
   l) $NR^{10}R^{11}$, and
   m) $O(CO)R^4$; and

2) aryl or heteroaryl, selected from:

phenyl, imidazole, isoxazole, oxazole, pyrazine, pyrazole, pyridazine, pyridine, pyrimidine, and thiazole, unsubstituted or substituted with one or more substituents independently selected from:

a) C_{1-6} alkyl,
b) C_{3-6} cycloalkyl,
c) $(F)_pC_{1-3}$ alkyl,
d) halogen,
e) OR^4,
f) CO_2R^4,
g) $(CO)NR^{10}R^{11}$,
h) $SO_2NR^{10}R^{11}$,
i) $N(R^{10})\ SO_2R^{11}$,
j) $S(O)_mR^4$,
k) CN,
l) $NR^{10}R^{11}$, and
m) $O(CO)R^4$;

R^2 is selected from:

1) H, C_0-C_6 alkyl, C_{3-6} cycloalkyl and heterocycle, unsubstituted or substituted with one or more substituents independently selected from:

a) C_{1-6} alkyl,
b) C_{3-6} cycloalkyl,
c) phenyl, unsubstituted or substituted with 1-5 substituents where the substituents are independently selected from R^4,
d) heteroaryl, unsubstituted or substituted with 1-5 substituents where the substituents are independently selected from R^4, and where heteroaryl is selected from:
benzimidazole, benzothiophene, furan, imidazole, indole, isoxazole, oxazole, pyrazine, pyrazole, pyridazine, pyridine, pyrimidine, pyrrole, thiazole, thiophene, and triazole;
e) heterocycle, unsubstituted or substituted with 1-5 substituents where the substituents are independently selected from R^4, and where heterocycle is selected from:

azetidine, imidazolidine, imidazoline, isoxazoline, isoxazolidine, morpholine, oxazoline, oxazolidine, oxetane, pyrazolidine, pyrazoline, pyrroline, tetrahydrofuran, tetrahydropyran, thiazoline, and thiazolidine;

f) $(F)_pC_{1-3}$ alkyl,
g) halogen,
h) OR^4,
i) $O(CH_2)_sOR^4$,
j) CO_2R^4,
k) CN,
l) $NR^{10}R^{11}$, and
m) $O(CO)R^4$;

2) aryl or heteroaryl, selected from:
phenyl, benzimidazole, benzothiophene, furan, imidazole, indole, isoxazole, oxazole, pyrazine, pyrazole, pyridazine, pyridine, pyrimidine, pyrrole, thiazole, thiophene, and triazole,
unsubstituted or substituted with one or more substituents independently selected from:

a) C_{1-6} alkyl,
b) C_{3-6} cycloalkyl,
c) $(F)_pC_{1-3}$ alkyl,
d) halogen,
e) OR^4,
f) CO_2R^4,
g) $(CO)NR^{10}R^{11}$,
h) $SO_2NR^{10}R^{11}$,
i) $N(R^{10})SO_2R^{11}$,
j) $S(O)_mR^4$,
k) CN,
l) $NR^{10}R^{11}$, and
m) $O(CO)R^4$;

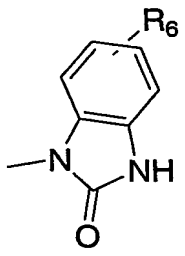
R^{10} and R^{11} are independently selected from: H, C_{1-6} alkyl, $(F)_pC_{1-6}$ alkyl, C_{3-6} cycloalkyl, aryl, heteroaryl and benzyl, unsubstituted or substituted with halogen, hydroxy or C_1-C_6 alkoxy, where R^{10} and R^{11} may be joined together to form a ring selected from: azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl and morpholinyl, which is unsubstituted or substituted with 1-5 substituents where the substituents are independently selected from R^4;

R^4 is independently selected from: H, C_{1-6} alkyl, $(F)_pC_{1-6}$ alkyl, C_{3-6} cycloalkyl, aryl, heteroaryl and benzyl, unsubstituted or substituted with halogen, hydroxy or C_1-C_6 alkoxy;

W is NR^4 or $C(R^4)_2$;

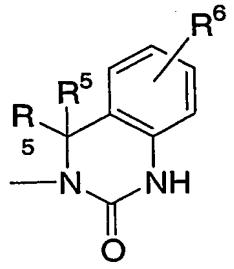
G-J is selected from:

N, such that when G-J is so defined the following structure forms:



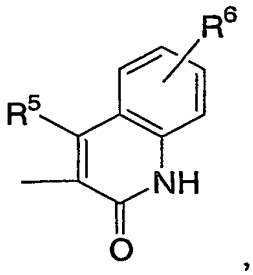
,

N-$C(R^5)_2$, such that when G-J is so defined the following structure forms:



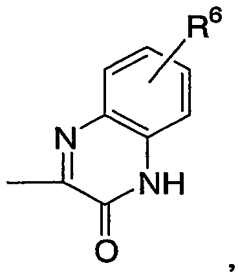
,

C=C(R^5), such that when G-J is so defined the following structure forms:



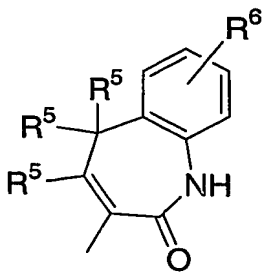
,

C=N, such that when G-J is so defined the following structure forms:



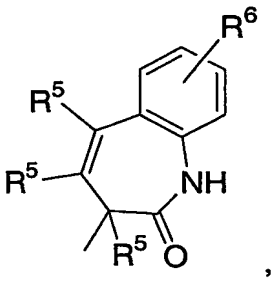
,

C=C(R^5)-C(R^5)$_2$, such that when G-J is so defined the following structure forms:



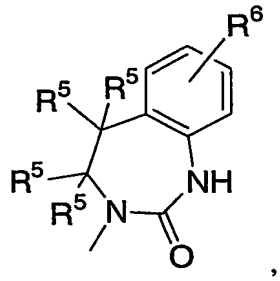
,

$C(R^5)$-$C(R^5)$=$C(R^5)$, such that when G-J is so defined the following structure forms:



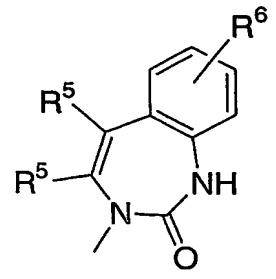
,

N-$C(R^5)_2$-$C(R^5)_2$, such that when G-J is so defined the following structure forms:



, and

N-$C(R^5)$=$C(R^5)$, such that when G-J is so defined the following structure forms:



;

R^6 is independently selected from H and:

a) C_{1-6} alkyl,
b) C_{3-6} cycloalkyl,
c) $(F)_pC_{1-3}$ alkyl,
d) halogen,
e) OR^4,
f) CO_2R^4,
g) $(CO)NR^{10}R^{11}$,
h) $SO_2NR^{10}R^{11}$,
i) $N(R^{10})\ SO_2R^{11}$,
j) $S(O)_mR^4$,
k) CN,
l) $NR^{10}R^{11}$, and
m) $O(CO)R^4$;

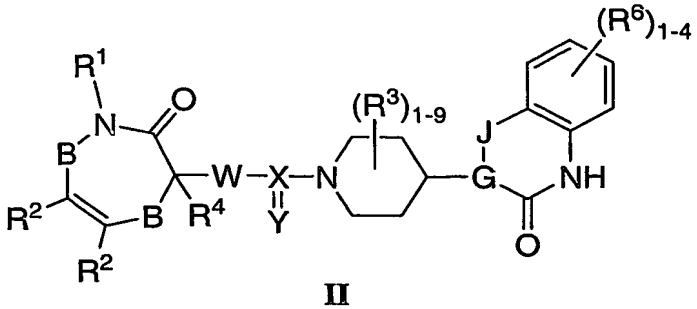
R^5 is independently selected from H, substituted or unsubstituted C_1-C_3 alkyl, CN, OR^4, $N(R^4)_2$ and CO_2R^4;

R^3 is independently selected from H, substituted or unsubstituted C_1-C_3 alkyl, F, CN and CO_2R^4;

p is 0 to 2q+1, for a substituent with q carbons
m is 0 to 2;
s is 1 to 3;

and pharmaceutically acceptable salts and individual stereoisomers thereof.

Another embodiment of the invention includes CGRP antagonists which include compounds of formula II:



II

wherein:

B, G, J, W, X, Y, R^1, R^2, R3, R4 and R6 are as defined in formula I,

and pharmaceutically acceptable salts and individual diastereomers thereof.

It is to be understood that where one or more of the above recited structures or substructures recite multiple substituents having the same designation each such variable may be the same or different from each similarly designated variable. For example, R^2 is recited four times in formula I, and each R^2 in formula I may independently be any of the substructures defined under R^2. The invention is not limited to structures and substructures wherein each R^2 must be the same for a given structure. The same is true with respect to any variable appearing multiple time in a structure or substructure.

The compounds of the present invention may contain one or more asymmetric centers and can thus occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. Additional asymmetric centers may be present depending upon the nature of the various substituents on the molecule. Each such asymmetric center will independently produce two optical isomers and it is intended that all of the possible optical isomers and diastereomers in mixtures and as pure or partially purified compounds are included within the ambit of this invention. The present invention is meant to comprehend all such isomeric forms of these compounds.

Some of the compounds described herein contain olefinic double bonds, and unless specified otherwise, are meant to include both E and Z geometric isomers.

The independent syntheses of these diastereomers or their chromatographic separations may be achieved as known in the art by appropriate modification of the methodology disclosed herein. Their absolute stereochemistry may be determined by the x-ray crystallography

of crystalline products or crystalline intermediates which are derivatized, if necessary, with a reagent containing an asymmetric center of known absolute configuration.

If desired, racemic mixtures of the compounds may be separated so that the individual enantiomers are isolated. The separation can be carried out by methods well known in the art, such as the coupling of a racemic mixture of compounds to an enantiomerically pure compound to form a diastereomeric mixture, followed by separation of the individual diastereomers by standard methods, such as fractional crystallization or chromatography. The coupling reaction is often the formation of salts using an enantiomerically pure acid or base. The diasteromeric derivatives may then be converted to the pure enantiomers by cleavage of the added chiral residue. The racemic mixture of the compounds can also be separated directly by chromatographic methods utilizing chiral stationary phases, which methods are well known in the art.

Alternatively, any enantiomer of a compound may be obtained by stereoselective synthesis using optically pure starting materials or reagents of known configuration by methods well known in the art.

As will be appreciated by those of skill in the art, not all of the R^{10} and R^{11} substituents are capable of forming a ring structure. Moreover, even those substituents capable of ring formation may or may not form a ring structure.

Also as appreciated by those of skill in the art, halo or halogen as used herein are intended to include chloro, fluoro, bromo and iodo.

As used herein, "alkyl" is intended to mean linear, branched and cyclic structures having no double or triple bonds. Thus C_{1-6}alkyl is defined to identify the group as having 1, 2, 3, 4, 5 or 6 carbons in a linear or branched arrangement, such that C_{1-6}alkyl specifically includes methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl, pentyl and hexyl. "Cycloalkyl" is an alkyl, part or all of which which forms a ring of three or more atoms. C_0 or C_0alkyl is defined to identify the presence of a direct covalent bond.

The term "alkenyl" means linear or branched structures and combinations thereof, of the indicated number of carbon atoms, having at least one carbon-to-carbon double bond, wherein hydrogen may be replaced by an additional carbon-to-carbon double bond. C_{2-6}alkenyl, for example, includes ethenyl, propenyl, 1-methylethenyl, butenyl and the like.

The term "alkynyl" means linear or branched structures and combinations thereof, of the indicated number of carbon atoms, having at least one carbon-to-carbon triple bond. Thus C_{2-6}alkynyl is defined to identify the group as having 2, 3, 4, 5 or 6 carbons in a linear or branched arrangement, such that C_{2-6}alkynyl specifically includes 2-hexynyl and 2-pentynyl.

As used herein, "aryl" is intended to mean any stable monocyclic or bicyclic carbon ring of up to 7 members in each ring, wherein at least one ring is aromatic. Examples of such aryl elements include phenyl, napthyl, tetrahydronapthyl, indanyl, or biphenyl.

The term "heterocycle" or "heterocyclic", as used herein except where noted, represents a stable 5- to 7-membered monocyclic- or stable 8- to 11-membered bicyclic heterocyclic ring system which is either saturated or unsaturated, and which consists of carbon atoms and from one to four heteroatoms selected from the group consisting of N, O and S, and wherein the nitrogen and sulfur heteroatoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a stable structure. Examples of such heterocyclic groups include, but are not limited to, azetidine, chroman, dihydrofuran, dihydropyran, dioxane, dioxolane, hexahydroazepine, imidazolidine, imidazolidinone, imidazoline, imidazolinone, indoline, isochroman, isoindoline, isothiazoline, isothiazolidine, isoxazoline, isoxazolidine, morpholine, morpholinone, oxazoline, oxazolidine, oxazolidinone, oxetane, 2-oxohexahydroazepin, 2-oxopiperazine, 2-oxopiperidine, 2-oxopyrrolidine, piperazine, piperidine, pyran, pyrazolidine, pyrazoline, pyrrolidine, pyrroline, quinuclidine, tetrahydrofuran, tetrahydropyran, thiamorpholine, thiazoline, thiazolidine, thiomorpholine and N-oxides thereof.

The term "heteroaryl", as used herein except where noted, represents a stable 5- to 7-membered monocyclic- or stable 9- to 10-membered fused bicyclic heterocyclic ring system which contains an aromatic ring, any ring of which may be saturated, such as piperidinyl, partially saturated, or unsaturated, such as pyridinyl, and which consists of carbon atoms and from one to four heteroatoms selected from the group consisting of N, O and S, and wherein the nitrogen and sulfur heteroatoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a stable structure. Examples of such heteroaryl groups include, but are not limited to, benzimidazole, benzisothiazole, benzisoxazole, benzofuran, benzothiazole, benzothiophene, benzotriazole, benzoxazole, carboline, cinnoline, furan, furazan, imidazole, indazole, indole, indolizine, isoquinoline, isothiazole, isoxazole, naphthyridine, oxadiazole, oxazole, phthalazine, pteridine, purine, pyran, pyrazine, pyrazole, pyridazine, pyridine, pyrimidine, pyrrole, quinazoline, quinoline, quinoxaline, tetrazole, thiadiazole, thiazole, thiophene, triazine, triazole, and N-oxides thereof.

The term "alkoxy," as in C_1-C_6 alkoxy, is intended to refer to include alkoxy groups of from 1 to 6 carbon atoms of a straight, branched and cyclic configuration. Examples include methoxy, ethoxy, propoxy, isopropoxy, cyclopropyloxy, cyclohexyloxy and the like.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

As used herein, "pharmaceutically acceptable salts" refer to derivatives wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, and the like.

The number of certain variables present in certain instances is defined in terms of the number of carbons present. For example, variable "p" is occasionally defined as follows: "p is 0 to 2q+1, for a substituent with q carbons". Where the substituent is "$(F)_pC_{1-3}$ alkyl" this means that when there is one carbon, there are 2(1) + 1 = 3 fluorines. When there are two carbons, there are 2(2) + 1 = 5 fluorines, and when thre are three carbons there are 2(3) = 1 = 7 fluorines.

When the compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid, and the like. In one aspect of the invention the salts are citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric, fumaric, and tartaric acids. It will be understood that,

as used herein, references to the compounds of Formula I are meant to also include the pharmaceutically acceptable salts.

Exemplifying the invention is the use of the compounds disclosed in the Examples and herein. Specific compounds within the present invention include a compound which selected from the group consisting of the compounds disclosed in the following Examples and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

The subject compounds are useful in a method of antagonism of CGRP receptors in a patient such as a mammal in need of such antagonism comprising the administration of an effective amount of the compound. The present invention is directed to the use of the compounds disclosed herein as antagonists of CGRP receptors. In addition to primates, especially humans, a variety of other mammals can be treated according to the method of the present invention.

Another embodiment of the present invention is directed to a method for the treatment, control, amelioration, or reduction of risk of a disease or disorder in which the CGRP receptor is involved in a patient that comprises administering to the patient a therapeutically effective amount of a compound that is an antagonist of CGRP receptors.

The present invention is further directed to a method for the manufacture of a medicament for antagonism of CGRP receptors activity in humans and animals comprising combining a compound of the present invention with a pharmaceutical carrier or diluent.

The subject treated in the present methods is generally a mammal, for example a human being, male or female, in whom antagonism of CGRP receptor activity is desired. The term "therapeutically effective amount" means the amount of the subject compound that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by the researcher, veterinarian, medical doctor or other clinician. As used herein, the term "treatment" refers both to the treatment and to the prevention or prophylactic therapy of the mentioned conditions, particularly in a patient who is predisposed to such disease or disorder.

The term "composition" as used herein is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts. Such term in relation to pharmaceutical composition, is intended to encompass a product comprising the active ingredient(s), and the inert ingredient(s) that make up the carrier, as well as any product which results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients.

Accordingly, the pharmaceutical compositions of the present invention encompass any composition made by admixing a compound of the present invention and a pharmaceutically acceptable carrier. By "pharmaceutically acceptable" it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The terms "administration of" and or "administering a" compound should be understood to mean providing a compound of the invention or a prodrug of a compound of the invention to the individual in need of treatment.

The utility of the compounds in accordance with the present invention as antagonists of CGRP receptor activity may be demonstrated by methodology known in the art. Inhibition of the binding of ^{125}I-CGRP to receptors and functional antagonism of CGRP receptors were determined as follows:

NATIVE RECEPTOR BINDING ASSAY: The binding of ^{125}I-CGRP to receptors in SK-N-MC cell membranes was carried out essentially as described (Edvinsson *et al.* (2001) *Eur. J. Pharmacol.* **415**, 39-44). Briefly, membranes (25 μg) were incubated in 1 ml of binding buffer [10 mM HEPES, pH 7.4, 5 mM $MgCl_2$ and 0.2% bovine serum albumin (BSA)] containing 10 pM ^{125}I-CGRP andantagonist. After incubation at room temperature for 3 h, the assay was terminated by filtration through GFB glass fibre filter plates (Millipore) that had been blocked with 0.5% polyethyleneimine for 3 h. The filters were washed three times with ice-cold assay buffer, then the plates were air dried. Scintillation fluid (50 μl) was added and the radioactivity was counted on a Topcount (Packard Instrument). Data analysis was carried out by using Prism and the K_i was determined by using the Cheng–Prusoff equation (Cheng & Prusoff (1973) *Biochem. Pharmacol.* **22**, 3099-3108).

NATIVE RECEPTOR FUNCTIONAL ASSAY: SK-N-MC cells were grown in minimal essential medium (MEM) supplemented with 10% fetal bovine serum, 2 mM L-glutamine, 0.1 mM non-essential amino acids, 1 mM sodium pyruvate, 100 units/ml penicillin and 100 μg/ml streptomycin at 37 °C, 95% humidity, and 5% CO_2. For cAMP assays, cells were plated at 5×10^5 cells/well in 96-well poly-D-lysine-coated plates (Becton-Dickinson) and cultured for ~ 18 h before assay. Cells were washed with phosphate-buffered saline (PBS, Sigma) then pre-incubated with 300 μM isobutylmethylxanthine in serum-free MEM for 30 min at 37 °C. Antagonist was added and the cells were incubated for 10 min before the addition of CGRP. The incubation was continued for another 15 min, then the cells were washed with PBS and processed for cAMP determination according to the manufacturer's recommended protocol. Maximal stimulation over basal was defined by using 100 nM CGRP. Dose–response curves

were generated by using Prism. Dose-ratios (DR) were calculated and used to construct full Schild plots (Arunlakshana & Schild (1959) *Br. J. Pharmacol.* **14**, 48-58).

RECOMBINANT RECEPTOR: Human CRLR (Genbank accession number L76380) was subcloned into the expression vector pIREShyg2 (BD Biosciences Clontech) as a 5'NheI and 3' PmeI fragment. Human RAMP1 (Genbank accession number AJ001014) was subcloned into the expression vector pIRESpuro2 (BD Biosciences Clontech) as a 5'NheI and 3'NotI fragment. 293 cells (human embryonic kidney cells; ATCC #CRL-1573) were cultured in DMEM with 4.5 g/L glucose, 1 mM sodium pyruvate and 2 mM glutamine supplemented with 10% fetal bovine serum (FBS), 100 units/mL penicillin and 100 ug/ml streptomycin, and maintained at 37^{0}C and 95% humidity. Cells were subcultured by treatment with 0.25% trypsin with 0.1% EDTA in HBSS. Stable cell line generation was accomplished by co-transfecting 10 ug of DNA with 30 ug Lipofectamine 2000 (Invitrogen) in 75 cm^2 flasks. CRLR and RAMP1 expression constructs were co-transfected in equal amounts. Twenty-four hours after transfection the cells were diluted and selective medium (growth medium + 300 ug/ml hygromycin and 1 ug/ml puromycin) was added the following day. A clonal cell line was generated by single cell deposition utilizing a FACS Vantage SE (Becton Dickinson). Growth medium was adjusted to 150 ug/ml hygromycin and 0.5 ug/ml puromycin for cell propagation.

RECOMBINANT RECEPTOR BINDING ASSAY: Cells expressing recombinant human CRLR/RAMP1 were washed with PBS and harvested in harvest buffer containing 50 mM HEPES, 1 mM EDTA and Complete protease inhibitors (Roche). The cell suspension was disrupted with a laboratory homogenizer and centrifuged at 48,000 g to isolate membranes. The pellets were resuspended in harvest buffer plus 250 mM sucrose and stored at –70°C. For binding assays, 10 ug of membranes were incubated in 1 ml binding buffer (10 mM HEPES, pH 7.4, 5 mM $MgCl_2$, and 0.2% BSA) for 3 hours at room temperature containing 10 pM ^{125}I-hCGRP (Amersham Biosciences) and antagonist. The assay was terminated by filtration through 96-well GFB glass fiber filter plates (Millipore) that had been blocked with 0.05% polyethyleneimine. The filters were washed 3 times with ice-cold assay buffer (10 mM HEPES, pH 7.4). Scintillation fluid was added and the plates were counted on a Topcount (Packard). Non-specific binding was determined and the data analysis was carried out with the apparent dissociation constant (K_i) determined by using a non-linear least squares fitting the bound CPM data to the equation below:

$$Y_{obsd} = \frac{(Y_{max} - Y_{min})(\%I_{max} - \%I_{min}/100) + Y_{min} + (Y_{max} - Y_{min})(100 - \%I_{max}/100)}{1 + ([Drug] / K_i (1 + [Radiolabel] / K_d)^{nH}}$$

Where Y is observed CPM bound, Y_{max} is total bound counts, Y min is non specific bound counts, (Y max – Y min) is specific bound counts, % I max is the maximum percent inhibition, % I min is the minimum percent inhibition, radiolabel is the probe, and the K_d is the apparent dissociation constant for the radioligand for the receptor as determined by Hot saturation experiments.

RECOMBINANT RECEPTOR FUNCTIONAL ASSAY: Cells were plated in complete growth medium at 85,000 cells/well in 96-well poly-D-lysine coated plates (Corning) and cultured for ~ 19 h before assay. Cells were washed with PBS and then incubated with inhibitor for 30 min at 37°C and 95% humidity in Cellgro Complete Serum-Free/Low-Protein medium (Mediatech, Inc.) with L-glutamine and 1 g/L BSA. Isobutyl-methylxanthine was added to the cells at a concentration of 300 μM and incubated for 30 min at 37°C. Human α-CGRP was added to the cells at a concentration of 0.3 nM and allowed to incubate at 37°C for 5 min. After α-CGRP stimulation the cells were washed with PBS and processed for cAMP determination utilizing the two-stage assay procedure according to the manufacturer's recommended protocol (cAMP SPA direct screening assay system; RPA 559; Amersham Biosciences). Dose response curves were plotted and IC_{50} values determined from a 4-parameter logistic fit as defined by the equation $y = ((a-d)/(1+(x/c)^b) + d$, where y = response, x = dose, a = max response, d = min response, c = inflection point and b = slope.

In particular, the compounds of the following examples had activity as antagonists of the CGRP receptor in the aforementioned assays, generally with a K_i or IC_{50} value of less than about 50 μM. Such a result is indicative of the intrinsic activity of the compounds in use as antagonists of CGRP receptors.

The ability of the compounds of the present invention to act as CGRP antagonists makes them useful pharmacological agents for disorders that involve CGRP in humans and animals, but particularly in humans.

The compounds of the present invention have utility in treating, preventing, ameliorating, controlling or reducing the risk of one or more of the following conditions or diseases: headache; migraine; cluster headache; chronic tension type headache; pain; chronic pain; neurogenic inflammation and inflammatory pain; neuropathic pain; eye pain; tooth pain; diabetes; non-insulin dependent diabetes mellitus; vascular disorders; inflammation; arthritis; bronchial hyperreactivity, asthma; shock; sepsis; opiate withdrawal syndrome; morphine tolerance; hot flashes in men and women; allergic dermatitis; psoriasis; encephalitis; brain trauma; epilepsy; neurodegenerative diseases; skin diseases; neurogenic cutaneous redness, skin

rosaceousness and erythema; inflammatory bowel disease, irritable bowel syndrome, cystitis; and other conditions that may be treated or prevented by antagonism of CGRP receptors. Of particular importance is the acute or prophylactic treatment of headache, including migraine and cluster headache.

The subject compounds are further useful in a method for the prevention, treatment, control, amelioration, or reduction of risk of the diseases, disorders and conditions noted herein.

The subject compounds are further useful in a method for the prevention, treatment, control, amelioration, or reduction of risk of the aforementioned diseases, disorders and conditions in combination with other agents.

The compounds of the present invention may be used in combination with one or more other drugs in the treatment, prevention, control, amelioration, or reduction of risk of diseases or conditions for which compounds of Formula I or the other drugs may have utility, where the combination of the drugs together are safer or more effective than either drug alone. Such other drug(s) may be administered, by a route and in an amount commonly used therefor, contemporaneously or sequentially with a compound of Formula I. When a compound of Formula I is used contemporaneously with one or more other drugs, a pharmaceutical composition in unit dosage form containing such other drugs and the compound of Formula I is preferred. However, the combination therapy may also include therapies in which the compound of Formula I and one or more other drugs are administered on different overlapping schedules. It is also contemplated that when used in combination with one or more other active ingredients, the compounds of the present invention and the other active ingredients may be used in lower doses than when each is used singly. Accordingly, the pharmaceutical compositions of the present invention include those that contain one or more other active ingredients, in addition to a compound of Formula I.

For example, the present compounds may be used in conjunction with an anti-inflammatory or analgesic agent or an anti-migraine agent, such as an ergotamine or 5-HT_1 agonists, especially a 5-$HT_{1B/1D}$ agonist, for example sumatriptan, naratriptan, zolmitriptan, eletriptan, almotriptan, frovatriptan, donitriptan, and rizatriptan; a cyclooxygenase inhibitor, such as a selective cyclooxygenase-2 inhibitor, for example rofecoxib, etoricoxib, celecoxib, valdecoxib or paracoxib; a non-steroidal anti-inflammatory agent or a cytokine-suppressing anti-inflammatory agent, for example with a compound such as aspirin, ibuprofen, ketoprofen, fenoprofen, naproxen, indomethacin, sulindac, meloxicam, piroxicam, tenoxicam, lornoxicam, ketorolac, etodolac, mefenamic acid, meclofenamic acid, flufenamic acid, tolfenamic acid,

diclofenac, oxaprozin, apazone, nimesulide, nabumetone, tenidap, etanercept, tolmetin, phenylbutazone, oxyphenbutazone, diflunisal, salsalate, olsalazine or sulfasalazine and the like; or a steroidal analgesic. Similarly, the instant compounds may be administered with a pain reliever such as acetaminophen, phenacetin, codeine, fentanyl, sufentanil, methadone, acetyl methadol, buprenorphine or morphine.

Additionally, the present compounds may be used in conjunction with an interleukin inhibitor, such as an interleukin-1 inhibitor; an NK-1 receptor antagonist, for example aprepitant; an NMDA antagonist; an NR2B antagonist; a bradykinin-1 receptor antagonist; an adenosine A1 receptor agonist; a sodium channel blocker, for example lamotrigine; an opiate agonist such as levomethadyl acetate or methadyl acetate; a lipoxygenase inhibitor, such as an inhibitor of 5-lipoxygenase; an alpha receptor antagonist, for example indoramin; an alpha receptor agonist; a vanilloid receptor antagonist; an mGluR5 agonist, antagonist or potentiator; a GABA A receptor modulator, for example acamprosate calcium; nicotinic antagonists or agonists including nicotine; muscarinic agonists or antagonists; a selective serotonin reuptake inhibitor, for example fluoxetine, paroxetine, sertraline, duloxetine, escitalopram, or citalopram; a tricyclic antidepressant, for example amitriptyline, doxepin, protriptyline, desipramine, trimipramine, or imipramine; a leukotriene antagonist, for example montelukast or zafirlukast; an inhibitor of nitric oxide or an inhibitor of the synthesis of nitric oxide.

Also, the present compounds may be used in conjunction with ergot alkaloids, for example ergotamine, ergonovine, ergonovine, methylergonovine, metergoline, ergoloid mesylates, dihydroergotamine, dihydroergocornine, dihydroergocristine, dihydroergocryptine, dihydro-α-ergocryptine, dihydro-β-ergocryptine, ergotoxine, ergocornine, ergocristine, ergocryptine, α-ergocryptine, β-ergocryptine, ergosine, ergostane, bromocriptine, or methysergide.

Additionally, the present compounds may be used in conjunction with a beta-adrenergic antagonist such as timolol, propanolol, atenolol, or nadolol, and the like; a MAO inhibitor, for example phenelzine; a calcium channel blocker, for example flunarizine, nimodipine, lomerizine, verapamil, nifedipine, prochlorperazine or gabapentin; neuroleptics such as olanzapine and quetiapine; an anticonvulsant such as topiramate, zonisamide, tonabersat, carabersat or divalproex sodium; an angiotensin II antagonist, for example losartan and candesartan cilexetil; an angiotensin converting enzyme inhibitor such as lisinopril; or botulinum toxin type A.

The present compounds may be used in conjunction with a potentiator such as caffeine, an H2-antagonist, simethicone, aluminum or magnesium hydroxide; a decongestant

such as phenylephrine, phenylpropanolamine, pseudoephedrine, oxymetazoline, epinephrine, naphazoline, xylometazoline, propylhexedrine, or levo-desoxy-ephedrine; an antitussive such as codeine, hydrocodone, caramiphen, carbetapentane, or dextromethorphan; a diuretic; a prokinetic agent such as metoclopramide or domperidone, and a sedating or non-sedating antihistamine.

In a particularly preferred embodiment the present compounds are used in conjunction with an anti-migraine agent, such as: an ergotamine; a 5-HT_1 agonist, especially a 5-$HT_{1B/1D}$ agonist, in particular, sumatriptan, naratriptan, zolmitriptan, eletriptan, almotriptan, frovatriptan, donitriptan and rizatriptan; and a cyclooxygenase inhibitor, such as a selective cyclooxygenase-2 inhibitor, in particular, rofecoxib, etoricoxib, celecoxib, meloxicam, valdecoxib or paracoxib.

The above combinations include combinations of a compound of the present invention not only with one other active compound, but also with two or more other active compounds. Likewise, compounds of the present invention may be used in combination with other drugs that are used in the prevention, treatment, control, amelioration, or reduction of risk of the diseases or conditions for which compounds of the present invention are useful. Such other drugs may be administered, by a route and in an amount commonly used therefor, contemporaneously or sequentially with a compound of the present invention. When a compound of the present invention is used contemporaneously with one or more other drugs, a pharmaceutical composition containing such other drugs in addition to the compound of the present invention is preferred. Accordingly, the pharmaceutical compositions of the present invention include those that also contain one or more other active ingredients, in addition to a compound of the present invention.

The weight ratio of the compound of the compound of the present invention to the other active ingredient(s) may be varied and will depend upon the effective dose of each ingredient. Generally, an effective dose of each will be used. Thus, for example, when a compound of the present invention is combined with another agent, the weight ratio of the compound of the present invention to the other agent will generally range from about 1000:1 to about 1:1000, or from about 200:1 to about 1:200. Combinations of a compound of the present invention and other active ingredients will generally also be within the aforementioned range, but in each case, an effective dose of each active ingredient should be used.

In such combinations the compound of the present invention and other active agents may be administered separately or in conjunction. In addition, the administration of one element may be prior to, concurrent to, or subsequent to the administration of other agent(s), and via the same or different routes of administration.

The compounds of the present invention may be administered by oral, parenteral (e.g., intramuscular, intraperitoneal, intravenous, ICV, intracisternal injection or infusion, subcutaneous injection, or implant), by inhalation spray, nasal, vaginal, rectal, sublingual, or topical routes of administration and may be formulated, alone or together, in suitable dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles appropriate for each route of administration. In addition to the treatment of warm-blooded animals the compounds of the invention are effective for use in humans.

The pharmaceutical compositions for the administration of the compounds of this invention may conveniently be presented in dosage unit form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the active ingredient into association with the carrier which constitutes one or more accessory ingredients. In general, the pharmaceutical compositions are prepared by uniformly and intimately bringing the active ingredient into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired formulation. In the pharmaceutical composition the active compound is included in an amount sufficient to produce the desired effect upon the process or condition of diseases. As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia; and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material

such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by the techniques described in the U.S. Patents 4,256,108; 4,166,452; and 4,265,874 to form osmotic therapeutic tablets for control release. Oral tablets may also be formulated for immediate release, such as fast melt tablets or wafers, rapid dissolve tablets or fast dissolve films.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxy-propylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl, p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally- occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents.

The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The compounds of the present invention may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

For topical use, creams, ointments, jellies, solutions or suspensions, etc., containing the compounds of the present invention are employed. Similarly, transdermal patches may also be used for topical administration.

The pharmaceutical composition and method of the present invention may further comprise other therapeutically active compounds as noted herein which are usually applied in the treatment of the above mentioned pathological conditions.

In the treatment, prevention, control, amelioration, or reduction of risk of conditions which require antagonism of CGRP receptor activity an appropriate dosage level will

generally be about 0.01 to 500 mg per kg patient body weight per day which can be administered in single or multiple doses. A suitable dosage level may be about 0.01 to 250 mg/kg per day, about 0.05 to 100 mg/kg per day, or about 0.1 to 50 mg/kg per day. Within this range the dosage may be 0.05 to 0.5, 0.5 to 5 or 5 to 50 mg/kg per day. For oral administration, the compositions are may be provided in the form of tablets containing 1.0 to 1000 milligrams of the active ingredient, particularly 1.0, 5.0, 10.0, 15.0. 20.0, 25.0, 50.0, 75.0, 100.0, 150.0, 200.0, 250.0, 300.0, 400.0, 500.0, 600.0, 750.0, 800.0, 900.0, and 1000.0 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. The compounds may be administered on a regimen of 1 to 4 times per day, or may be administered once or twice per day.

When treating, preventing, controlling, ameliorating, or reducing the risk of headache, migraine, cluster headache, or other diseases for which compounds of the present invention are indicated, generally satisfactory results are obtained when the compounds of the present invention are administered at a daily dosage of from about 0.1 milligram to about 100 milligram per kilogram of animal body weight, given as a single daily dose or in divided doses two to six times a day, or in sustained release form. For most large mammals, the total daily dosage is from about 1.0 milligrams to about 1000 milligrams, or from about 1 milligrams to about 50 milligrams. In the case of a 70 kg adult human, the total daily dose will generally be from about 7 milligrams to about 350 milligrams. This dosage regimen may be adjusted to provide the optimal therapeutic response.

It will be understood, however, that the specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

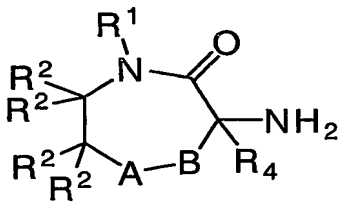
Several methods for preparing the compounds of this invention are illustrated in the following Schemes and Examples. Starting materials are made according to procedures known in the art or as illustrated herein.

The compounds of the present invention can be prepared readily according to the following Schemes and specific examples, or modifications thereof, using readily available starting materials, reagents and conventional synthesis procedures. In these reactions, it is also possible to make use of variants which are themselves known to those of ordinary skill in this art but are not mentioned in greater detail. The general procedures for making the compounds

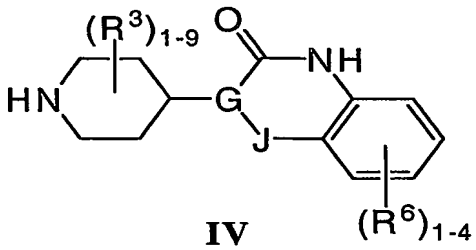
claimed in this invention can be readily understood and appreciated by one skilled in the art from viewing the following Schemes.

The synthesis of caprolactam benzimidazolone intermediates may be conducted as described in Schemes 1-12

The preparation of final compounds proceeds through intermediates such as those of Formula **III** and Formula **IV**, and the synthesis of each intermediate is described herein.



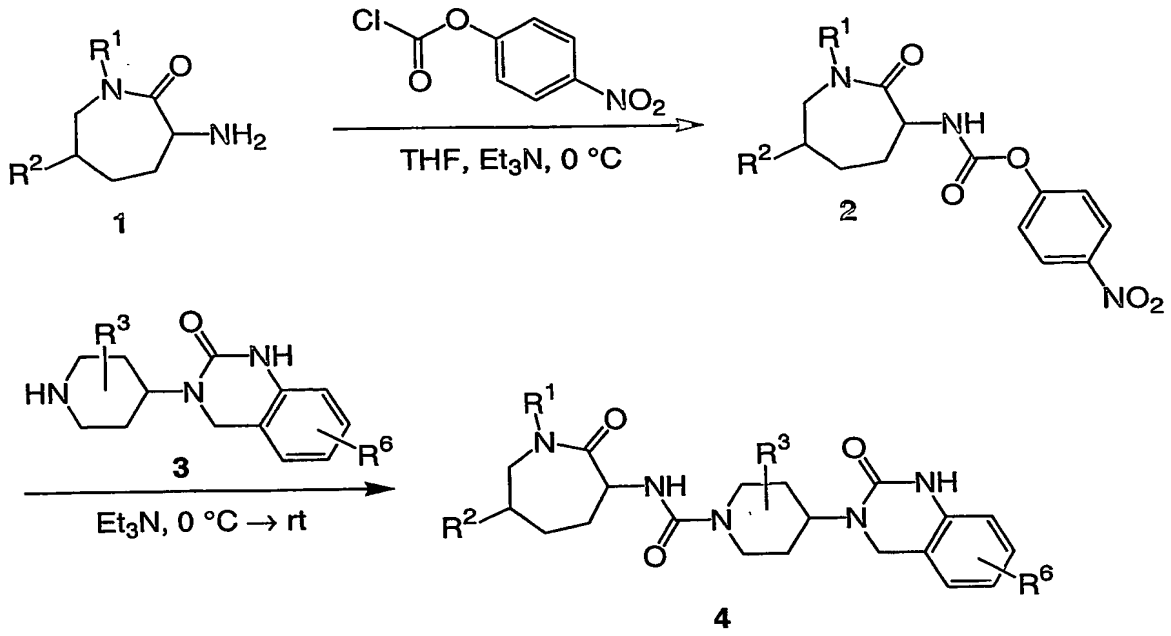
III



IV

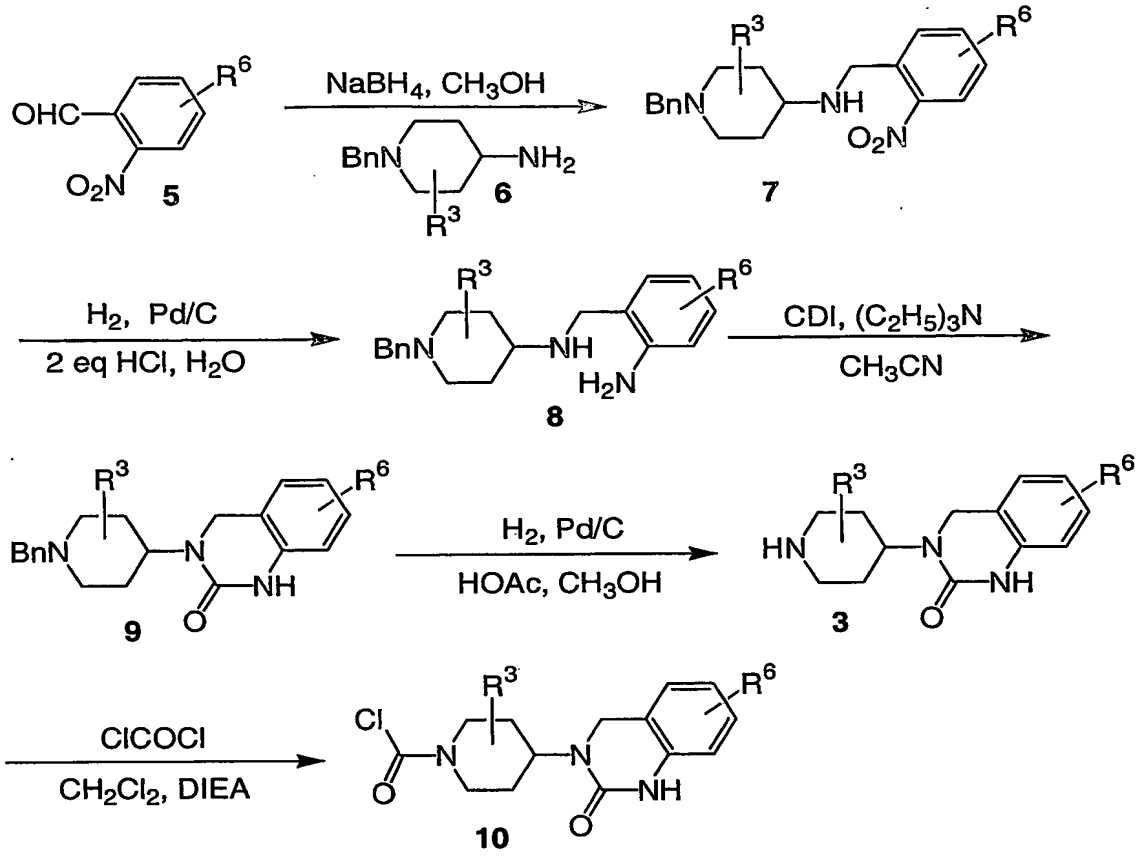
In general, intermediates of the Formulae **III** and **IV** can be coupled through a urea linkage as shown in Scheme 1. Amine intermediate **1** can be converted to a reactive carbamate, for example p-nitrophenylcarbamate **2**, which is subsequently reacted with an amine like that of intermediate **3** to produce urea **4**. Other activated intermediates known to those skilled in the art can be used to prepare compounds such as **4**. For example, amine **1** can be directly acylated with the appropriate carbamoyl chloride.

SCHEME 1



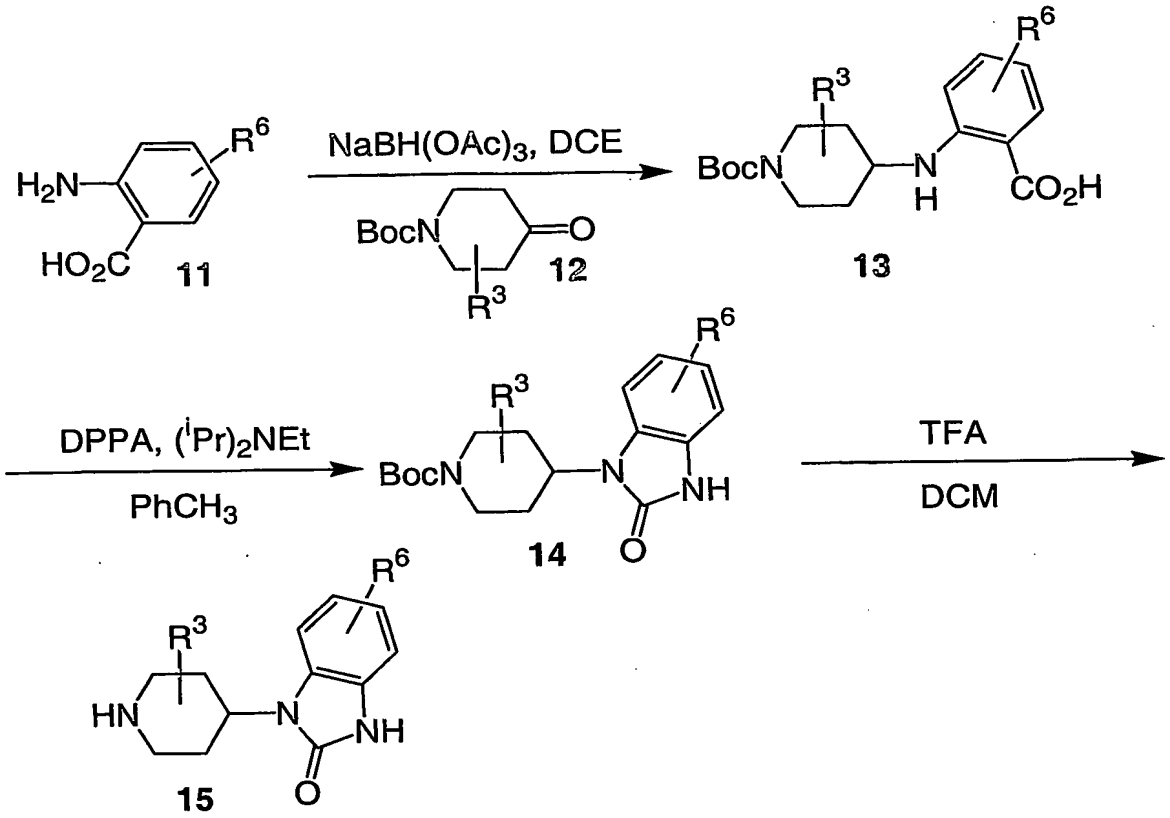
The intermediate **3** can be prepared according to the general method described by Takai et al., Chem. Pharm. Bull. 1985, 33, 1116-1128 illustrated in Scheme 2. The carbamoyl chloride **10** can be formed by reacting the amine with phosgene.

SCHEME 2



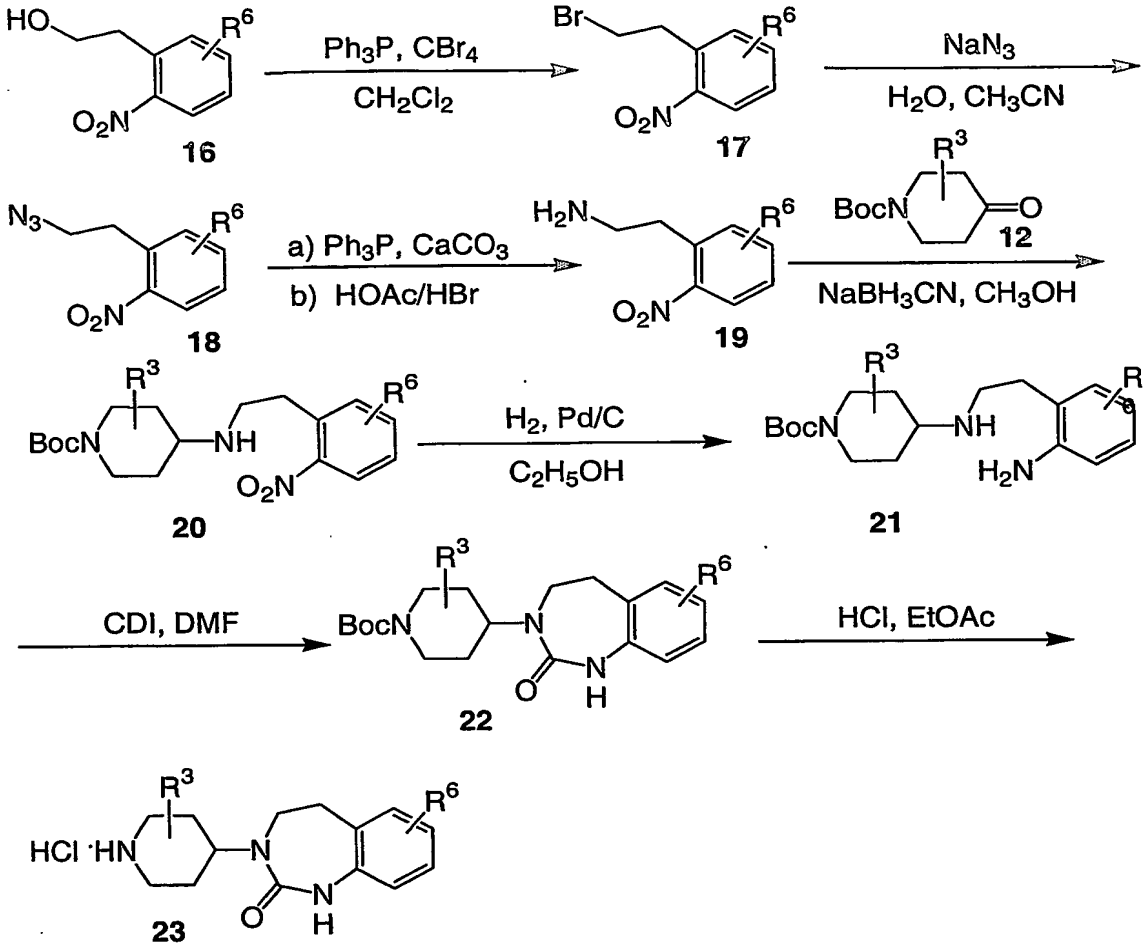
The synthesis of 4-piperidinyl-1-benzimidazolones of the general formula **15** can be accomplished by procedures similar to those described in Henning et al., J. Med. Chem., 1987, 30, 814-819, and references cited therein. Alternatively, an anthranilic acid derivative, such as **11** in Scheme 3, can be reductively alkylated with ketones such as **12** to give the monalkylated product **13**. Curtius rearrangement with concomitant ring closure furnishes imidazolone **14**. Final deprotection under standard conditions gives the final product **15**.

SCHEME 3



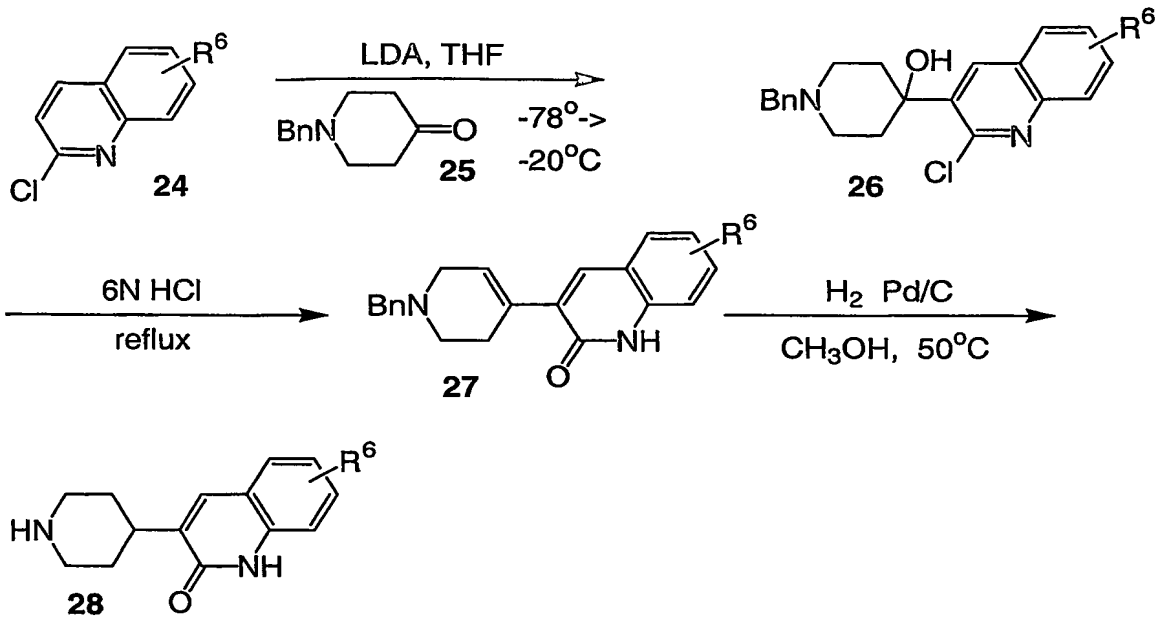
A similar synthetic strategy can be used to construct the related benzodiazepinone of formula **23**. The starting alcohols **16** are commercially available, or prepared according to procedures known to those skilled in the art. Alcohol **16** can be converted to a halide using standard conditions, such as triphenylphosphine and bromine to prepare the bromide **17**. The halide is displaced with azide nucleophile, and the azide **18** reduced under standard conditions to give the primary amine **19**. This amine can be reductively alkylated with a suitably protected 4-piperidinone to give compound **20**. Reduction of the nitro group is easily accomplished using a variety of conditions, and subsequent cyclization can be achieved with carbonyldiimidazole to afford cyclic urea **22**. Deprotection then liberates amine **23**.

SCHEME 4



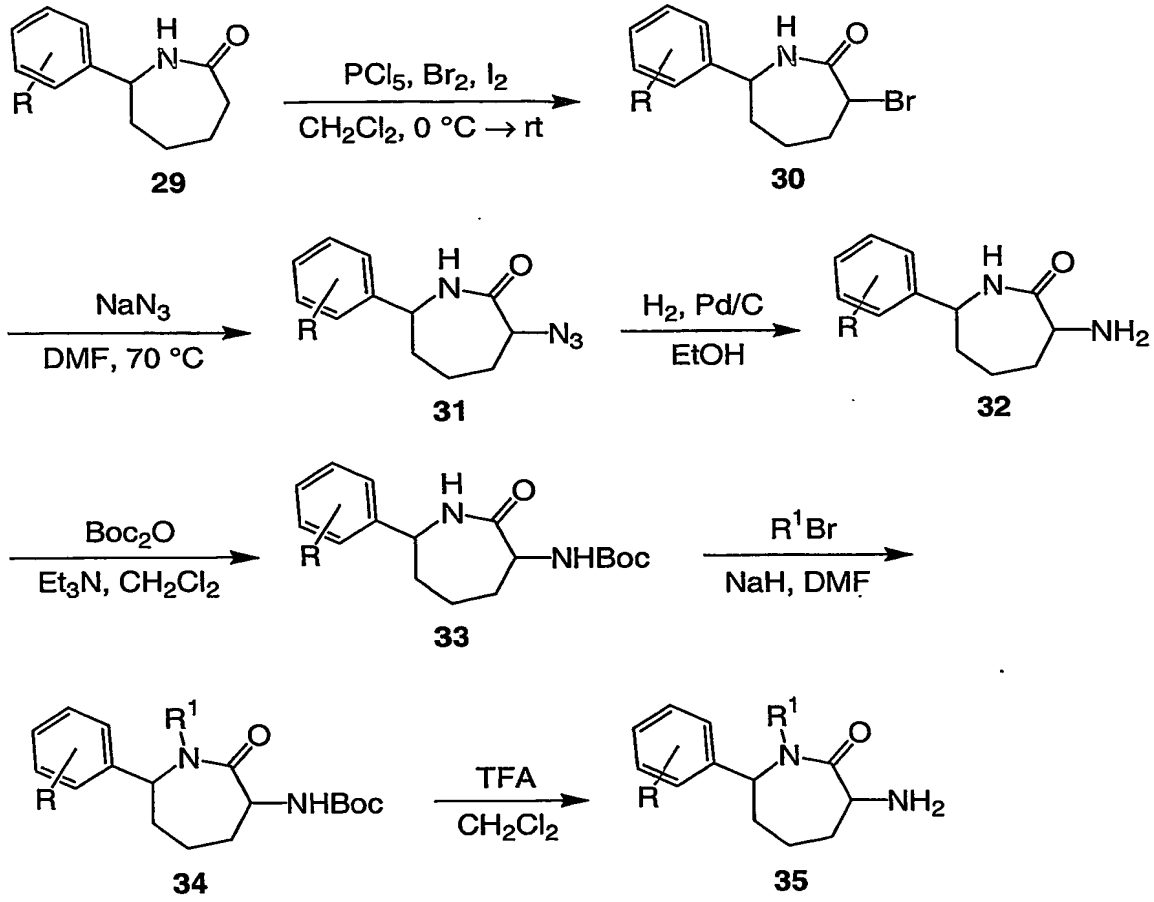
Quinolone **28** can be prepared by reaction of the anion derived from 2-chloroquinoline and lithium diisopropylamide, with piperidone **25** (Scheme 5). Concommitant elimination of the tertiary alcohol and hydrolysis of the chloroquinoline is accomplished with aqueous hydrochloric acid. Removal of the piperidine *N*-benzyl protective group by catalytic hydrogenation also reduces the olefin formed in the previous step and results in amine **28**.

SCHEME 5



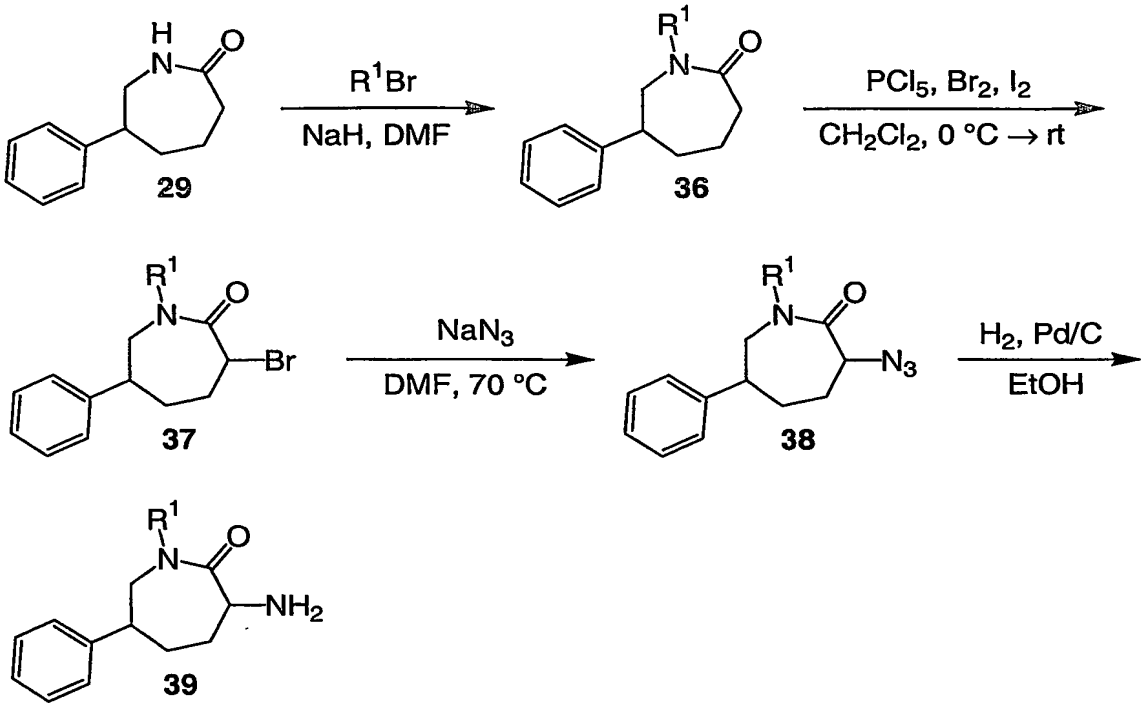
Lactam **29** (Scheme 6) can be prepared according to known procedures (J. Med. Chem., 1988, 31, 422-428). After bromination and displacement with sodium azide, hydrogenation under standard conditions yields amine **32**. Protection of the primary amine allows for selective alkylation of the amide nitrogen with various electrophiles, for example alkyl bromides, and deprotection and of the primary amine can be accomplished under acidic conditions, affording compounds of the general formula **35**.

SCHEME 6



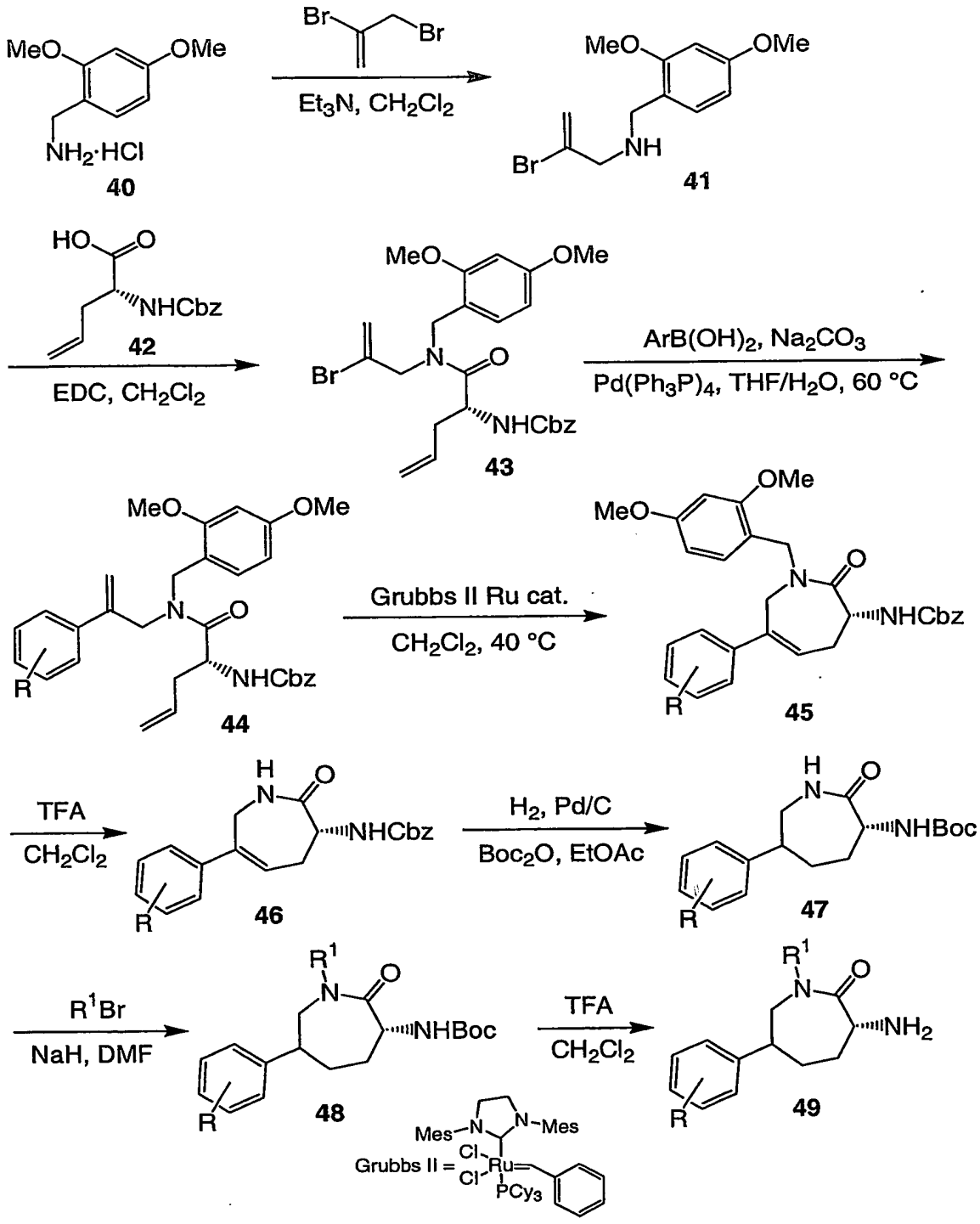
Lactam **29** can be prepared according to known procedures (J. Med. Chem., 1988, 31, 422-428) (Scheme 7). Using sodium hydride as the base, the amide can be alkylated with various electrophiles such as alkyl bromides. Bromination with phosphorus pentachloride and liquid bromine gives the corresponding bromide, which is reacted with sodium azide and finally reduced under standard hydrogenation conditions, yielding amine compounds of the general formula **39**.

SCHEME 7



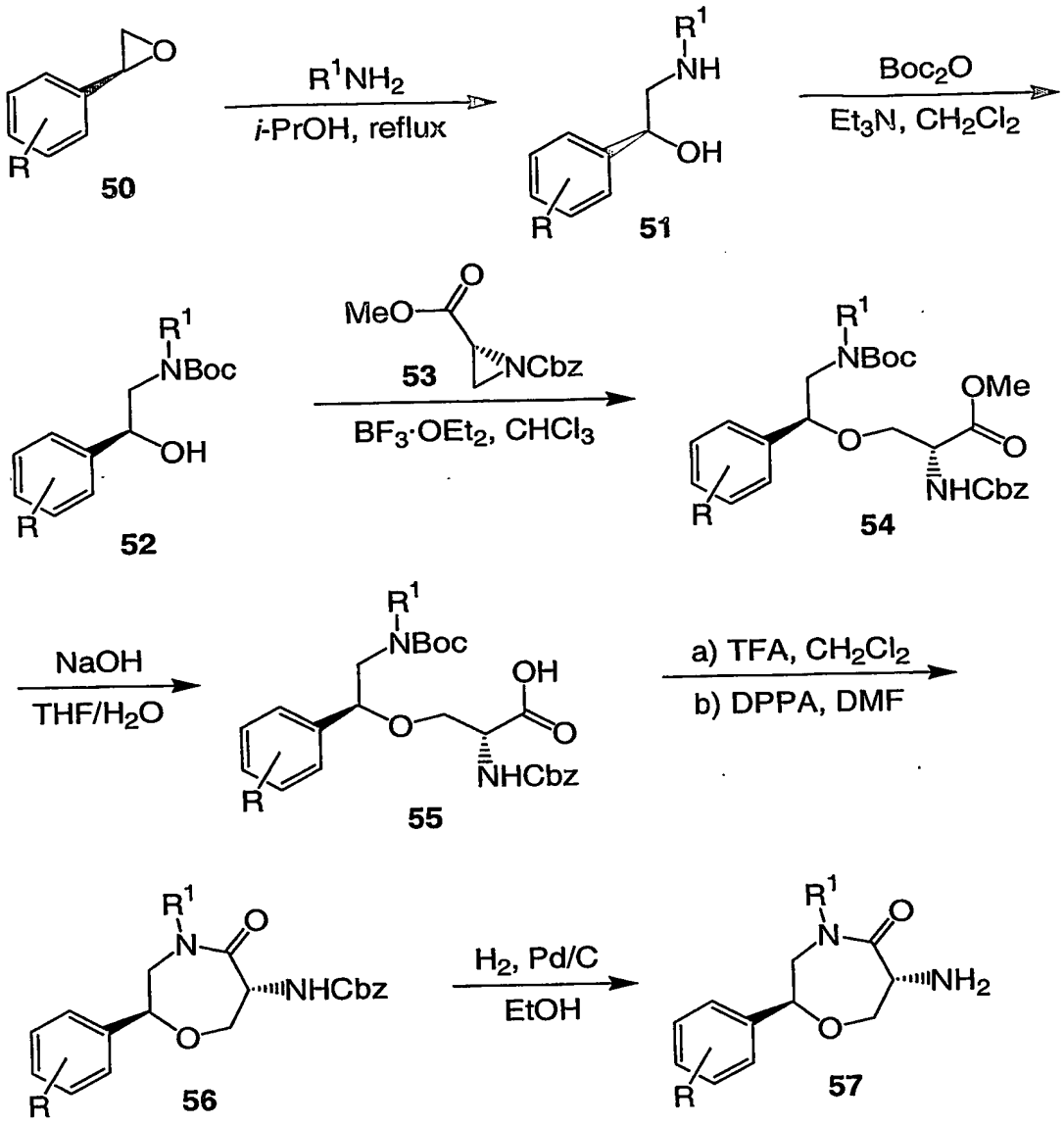
Alternatively, caprolactams can be assembled following an olefin metathesis strategy as outlined in Scheme 8. 2,4-Dimethoxybenzylamine hydrochloride is alkylated with 2,3-dibromopropene under mild basic conditions to give amine **41**. (2*R*)-2-{[(benzyloxy)carbonyl]amino}pent-4-enoic acid **42**, prepared in one step from commercially available D-allyl glycine according to known procedures (J. Chem. Soc., 1962, 3963-3968), can be coupled to amine **41** under a variety of conditions to give amide **43**. A variety of transition metal catalized cross couplings can be performed on the vinyl bromide, for example palladium-mediated arylations with phenylboronic acid and sodium carbonate, yielding styrene derivative **44**. Ring-closing metathesis occurs in the presence of the Grubbs second generation ruthenium catalyst in dichloromethane with mild heating to afford lactam **45**. Removal of the dimethoxybenzyl group and hydrogenation with *in situ* protection of the primary amine gives the corresponding saturated lactam **47**. After selective alkylation of the amide nitrogen with various electrophiles such as alkyl bromides, deprotection under acidic conditions yields compounds of the general formula **49**.

SCHEME 8


MeO
OMe
NH2·HCl
40
Br
Br
Et3N, CH2Cl2
NH
41
HO
O
NHCbz
42
EDC, CH2Cl2
N
43
ArB(OH)2, Na2CO3
Pd(Ph3P)4, THF/H2O, 60 °C
R
44
Grubbs II Ru cat.
CH2Cl2, 40 °C
45
TFA
CH2Cl2
H
46
H2, Pd/C
Boc2O, EtOAc
NHBoc
47
R1Br
NaH, DMF
48
TFA
CH2Cl2
NH2
49
Grubbs II =
Mes
N-Mes
Cl
Ru
PCy3

The oxazepanones can be prepared according to Scheme 9. (*S*)-(-)-Styrene oxide (or substituted derivatives) can be opened by reaction with various primary amines in isopropanol solvent to afford the corresponding amino alcohols **51**. Selective *N*-protection followed by boron trifluoride etherate catalized aziridine opening of **53** (prepared according to known procedures: J. Chem. Soc., Perkins Trans. 1, 1994, 7, 807-816) provides ether **54**. Hydrolysis of the methyl ester, selective amine deprotection, and amide bond formation with diphenylphosphoryl azide gives **56**, which after standard hydrogenation conditions yields amine **57**.

SCHEME 9

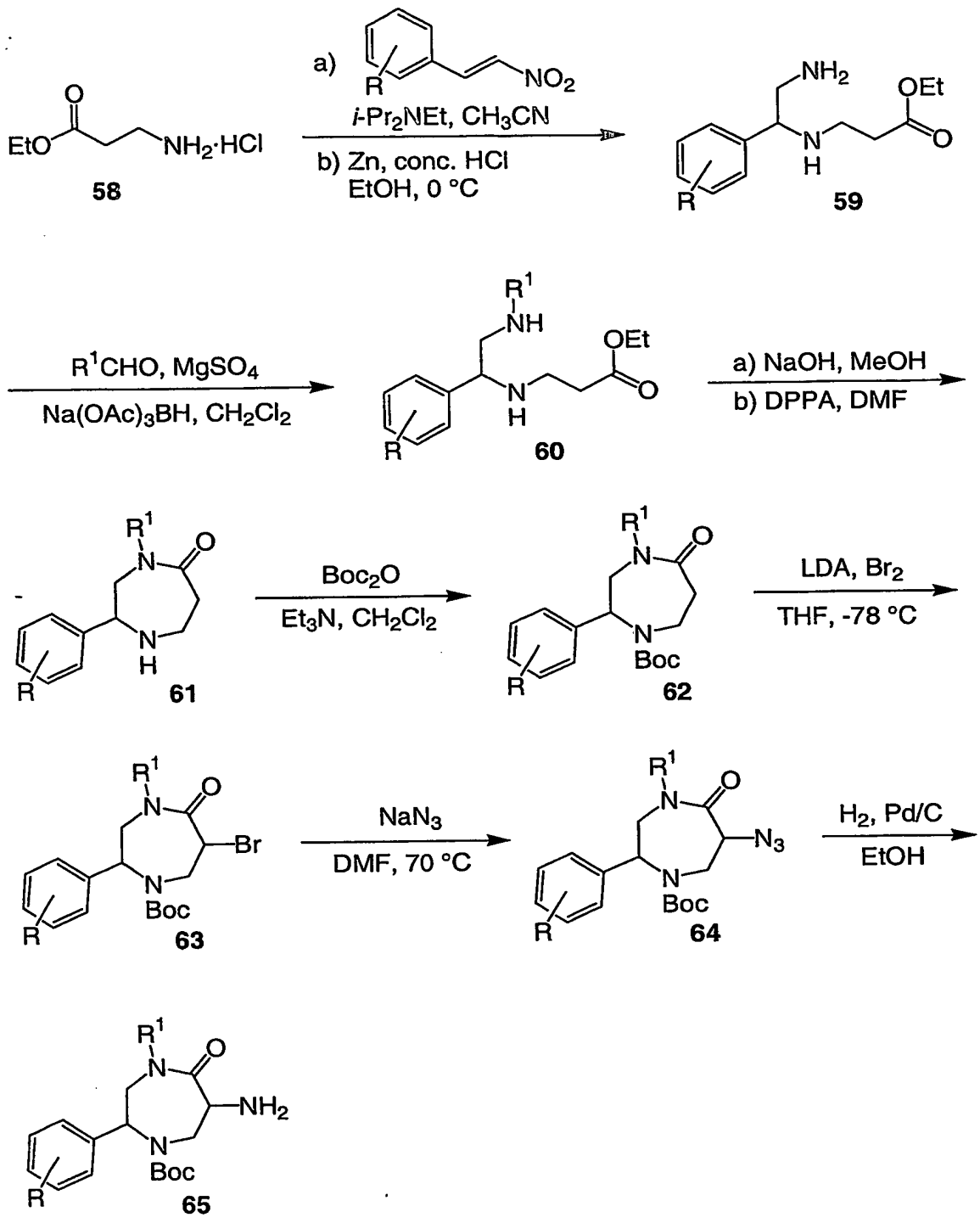


Diazepanone analogs of the parent caprolactams are prepared as follows in Scheme **10**. Michael addition of ethyl 3-aminopropanoate hydrochloride to *trans*-β-nitrostyrene (or substituted derivatives) and immediate nitro group reduction with acidic zinc suspension gives diamine **59**. Selective reductive alkylation of the primary amine can be performed with various aldehydes and sodium triacetoxyborohydride. Ester hydrolysis and ring closure yields diazepanones **61**. After amine protection, bromination is accomplished by enolate generation with lithium diisopropylamide and subsequent quenching with liquid bromine at low

temperatures. Displacement of the bromide with sodium azide and hydrogenation under standard conditions yield amines of the general formula **65**.

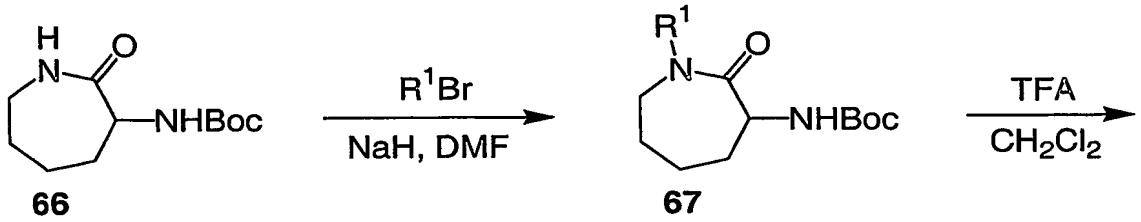
SCHEME 10

5

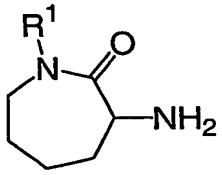

EtO
NH2·HCl
58
a)
NO2
i-Pr2NEt, CH3CN
b) Zn, conc. HCl
EtOH, 0 °C
NH2
OEt
N
H
59
R1CHO, MgSO4
Na(OAc)3BH, CH2Cl2
R1
NH
60
a) NaOH, MeOH
b) DPPA, DMF
61
Boc2O
Et3N, CH2Cl2
Boc
62
LDA, Br2
THF, -78 °C
Br
63
NaN3
DMF, 70 °C
N3
64
H2, Pd/C
EtOH
NH2
65

Commercially available lactam **66** can be selectively alkylated with a variety of electrophiles such as alkyl bromides to give amide **67**. Removal of the protective group under acidic conditions affords amines of the general formula **68**.

SCHEME 11



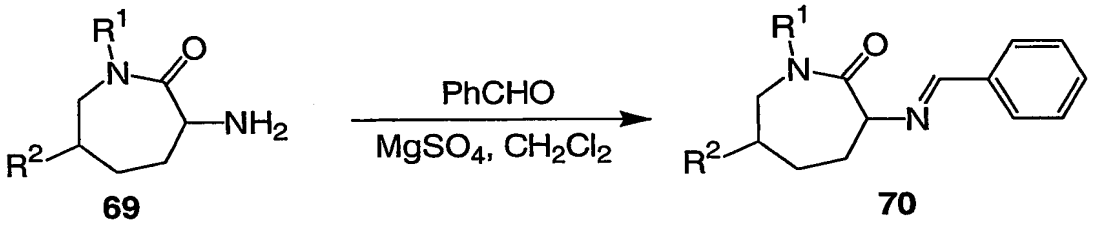
66 **67**



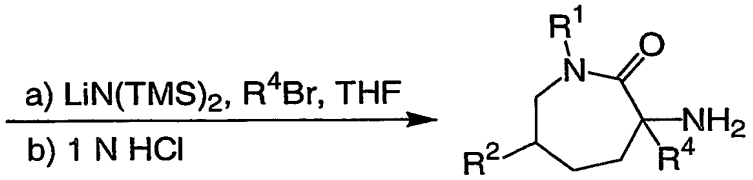
68

Alkyl substituted caprolactams **69** can be condensed with benzaldehyde to form the imine in the presence of magnesium sulfate. Deprotonation with lithium bis(trimethylsilyl)amide, follwed by quenching with electrophiles, for example alkyl bromides, and acid catalyzed imine hydrolysis gives substituted caprolactams of the general formula **71**.

SCHEME 12



69 **70**



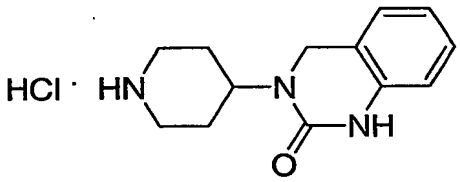
71

In some cases the final product may be further modified, for example, by manipulation of substituents. These manipulations may include, but are not limited to, reduction, oxidation, alkylation, acylation, and hydrolysis reactions which are commonly known to those skilled in the art.

In some cases the order of carrying out the foregoing reaction schemes may be varied to facilitate the reaction or to avoid unwanted reaction products. The following examples are provided so that the invention might be more fully understood. These examples are illustrative only and should not be construed as limiting the invention in any way.

EXAMPLES

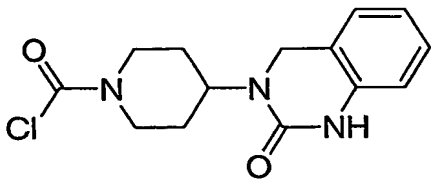
INTERMEDIATE 1



3-(4-Piperidinyl)-3,4-dihydroquinazolin-2(1*H*)-one hydrochloride

The title compound was prepared according to the procedure described by H. Takai et al., in Chem. Pharm. Bulletin 1985, 33(3) 1116-1128. ^{1}H NMR (500 MHz, DMSO-d6) δ 9.31 (s, 1H), 8.79 (br s, 1H), 8.58 (br s, 1H), 7.13 (t, J = 8 Hz, 2H), 6.88 (t, J = 8 Hz, 1H), 6.77 (d, J = 8 Hz, 1H), 4.37 (tt, J = 12, 4 Hz, 1H), 4.29 (s, 2H), 3.00 (q, J = 11 Hz, 2H), 2.06 (dq, J = 4, 12 Hz, 2H), 1.73 (d, J = 12 Hz, 2H).

INTERMEDIATE 2

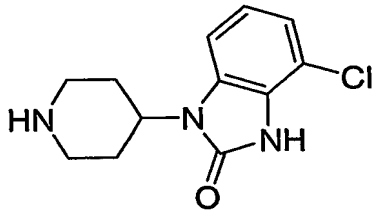


3-(1-Chlorocarbonyl-4-piperidinyl)-3,4-dihydroquinazolin-2(1*H*)-one

Intermediate 1 (493 mg, 1.84 mmol) was suspended in saturated sodium carbonate (10 mL) and extracted with methylene chloride (3 x 40 mL). The organic phase was washed

with saturated brine and dried over sodium sulfate. The free base thus obtained (422 mg, 1.82 mmol) was dissolved in methylene chloride (50 mL), diisopropylethylamine was added (0.32 mL, 1.82 mmol), and the solution cooled to 0°C under argon. A 20% solution of phosgene in toluene (4.8 mL, 9.1 mmol) was added slowly over 10 min. The reaction was warmed to room temperature and stirred for 2.5 h. The solvent and excess reagent were removed in vacuo, and the resulting white solid partitioned between methylene chloride and half-saturated sodium chloride solution. The organic phase was dried over magnesium sulfate. The title compound was obtained as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19 (t, J = 8 Hz, 1H), 7.08 (d, J = 8 Hz, 1H), 6.97 (t, J = 8 Hz, 1H), 6.86 (br s, 1H), 6.68 (d, J = 8 Hz, 1H), 4.70 (pentet, J = 2 Hz, 1H), 4.48 (t, J = 2 Hz, 2H), 3.20 (m, 1H), 3.00 (m, 1H), 1.83 (s, 4H).

INTERMEDIATE 3



4-Chloro-1-piperidin-4-yl-1,3-dihydro-2*H*-benzimidazol-2-one

Step A. 2-{[1-(*tert*-Butoxycarbonyl)piperidin-4-yl]amino}-6-chlorobenzoic acid Sodium triacetoxyborohydride (3.09 g, 14.6 mmol) was added to a solution of 2-amino-6-chlorobenzoic acid (1.00 g, 5.83 mmol) and N-(t-butoxycarbonyl)-4-piperidone (2.32 g, 11.7 mmol) in dichloroethane (20 mL) at room temperature. After 5 h, the reaction was quenched with saturated aqueous ammonium chloride. This mixture was separated and extracted with ethyl acetate (3x). After drying over sodium sulfate, the solution was filtered and evaporated to give the crude product. This was purified by chromatography (silica gel, 0 to 15% methanol in methylene chloride gradient elution), which gave the title compound contaminated with some ketone starting material (3.60 g). MS 335.1 (M+1).

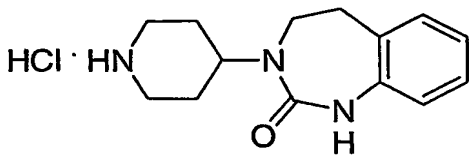
Step B. *tert*-Butyl 4-(4-chloro-2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)piperidine-1-carboxylate Diphenylphosphoryl azide (1.71 g, 6.20 mmol) and *N*,*N*-diisopropylethylamine (0.80 g, 6.20 mmol) were added to a solution of a portion of the material from Step A (2.00 g, <5.64 mmol) in toluene (20 mL) at room temperature. After 30 min the solution was heated to 80 °C. After 2 h, the toluene was evaporated in vacuo, the residue partitioned between water and

ethyl acetate, and the organic phase dried over magnesium sulfate. The crude product was purified by chromatography (silica gel, 0 to 10% methanol in methylene chloride gradient elution), which gave the title compound (2.17 g). MS 374.1 (M+Na).

Step C. 4-Chloro-1-piperidin-4-yl-1,3-dihydro-2*H*-benzimidazol-2-one

tert-butyl 4-(4-chloro-2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)piperidine-1-carboxylate from Step B (2.17 g, <6.17 mmol) was dissolved in dichloromethane (10 mL) and trifluoacetic acid (5 mL) was added at room temperature. After 5h, additional trifluoacetic acid (5 mL) was added and the reaction stirred overnight. To this solution was added 2.0 M ammonia in methanol, the mixture was filtered and the volatiles removed in vacuo. The crude product was purified by chromatography (silica gel, 1 to 25% methanol containing 1% NH_3 in methylene chloride gradient elution), which gave the title compound (1.12 g). MS 352.2 (M+1).

INTERMEDIATE 4



3-(4-Piperidinyl)-1,3,4,5-tetrahydro-2*H*-1,3-benzodiazapin-2-one hydrochloride

Step A. 2-(2-Bromoethyl)nitrobenzene

Triphenylphosphine (39.2 g, 0.150 mol) and carbon tetrabromide (49.5 g, 0.150 mol) were added sequentially to a solution of 2-(2-hydroxyethyl)-nitrobenzene (25.0 g, 0.150 mol) in methylene chloride (400 mL) at 0°C. The reaction was stirred overnight and quenched with saturated sodium bicarbonate solution. The methylene chloride phase was washed with saturated brine and dried over magnesium sulfate. The crude product was treated with ethyl acetate, and the precipitated triphenylphosphine oxide removed by filtration. Further purification by flash chromatography by (silica gel, 0-10% ethyl acetate in hexane gradient elution) produced the title compound (27.9 g).

Step B. 2-(2-Azidoethyl)nitrobenzene

Sodium azide (22.8, 0.351 mol) in water (60 mL) was added to a solution of 2-(2-bromoethyl)-nitrobenzene (27.9 g, 0.121 mol) in acetonitrile (120 mL). The reaction was refluxed for 4 h, cooled, and partitioned between methylene chloride and water. The organic

phase was washed with saturated brine, and dried over magnesium sulfate. The title compound was obtained as an oil (22.8g).

Step C. 2-(2-Aminoethyl)nitrobenzene

Triphenylphosphine (31.1 g, 0.118 mol) and calcium carbonate (50 mg, 0.5 mmol) were added to a solution of 2-(2-azidoethyl)nitrobenzene (22.8 g, 0.118 mol) in benzene (500 mL). The reaction was stirred at room temperature until complete. The solvent was removed in vacuo, and the residue treated with acetic acid (100 mL) and 48% hydrogen bromide (100 mL) at 100°C for 1 h. The reaction was cooled and concentrated. Water was added and the solution extracted with methylene chloride. The aqueous layer was made basic by the addition of 5% aqueous sodium hydroxide solution, then extracted with ethyl acetate. The organic phase was washed with saturated brine and dried over sodium sulfate. The title compound was obtained as an oil (8.0 g). MS 167 (M+1).

Step D. *t*-Butyl 4-{[2-(2-nitrophenyl)ethyl]amino}piperidine-1-carboxylate

A solution of 2-(2-aminoethyl)nitrobenzene (8.00 g, 48.1 mmol) and 1-*t*-butoxycarbonyl-4-piperidinone (9.59 g, 48.1 mmol) in methanol (100 mL) was brought to pH 5 by the addition of acetic acid. Sodium cyanoborohydride (4.53 g, 72.2 mmol) was added and the reaction stirred for 3 h. Methanol was removed in vacuo, and the residue partitioned between ethyl acetate and saturated sodium bicarbonate solution. The organic phase was washed with saturated brine and dried over sodium sulfate. The title compound was obtained as an oil (19.27 g). MS 350 (M+1).

Step E. *t*-Butyl 4-{[2-(2-aminophenyl)ethyl]amino}piperidine-1-carboxylate

tert-Butyl 4-{[2-(2-nitrophenyl)ethyl]amino}piperidine-1-carboxylate and 10% palladium on carbon (1.9 g) were stirred in ethanol (250 mL) overnight under one atmosphere hydrogen. Catalyst was filtered from the solution and solvent removed in vacuo to provide the title compound (17.2 g). MS 320 (M+1)

Step F. 3-(1-*t*-Butoxycarbonyl-4-piperidinyl)-1,3,4,5-tetrahydro-2*H*-1,3-benzodiazapin-2-one

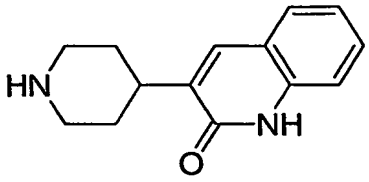
Carbonyldiimidazole (8.73 g, 53.8 mmol) was added to a solution of *tert*-butyl 4-{[2-(2-aminophenyl)ethyl]amino}piperidine-1-carboxylate (17.2 g, 53.8 mmol) in dimethylformamide (200 mL), and stirred at room temperature for 2 h. The reaction was diluted with ethyl acetate and extracted with water, then saturated brine. The crude product was purified

by chromatography (silica gel, 0-30% ethyl acetate in methylene chloride gradient elution). The title compound was obtained as a dark solid (4.8 g).

Step G. 3-(4-Piperidinyl)-1,3,4,5-tetrahydro-2*H*-1,3-benzodiazapin-2-one hydrochloride

A solution of 3-(1-*t*-butoxycarbonyl-4-piperidinyl)-1,3,4,5-tetrahydro-2*H*-1,3-benzodiazapin-2-one (4.80 g, 13.9 mmol) in ethyl acetate (300 mL) was saturated with hydrogen chloride gas at 0°C. The reaction was allowed to warm to room temperature and stirred overnight. The solid was filtered and washed with ethyl acetate. The ethyl acetate filtrate was concentrated for a second crop. The title compound was obtained as a solid (2.94 g). MS 246 (M+1). ^{1}H NMR (500 MHz, CD_3OD) δ 7.10 (m, 2H), 6.94 (d, J = 8 Hz, 1H), 6.91 (t, J = 8 Hz, 1H), 4.35 (tt, J = 10, 1 Hz, 1H), 3.52 (m, 4H), 3.12 (t, J = 12 Hz, 2H), 3.05 (m, 2H), 2.07 (qd, J = 12, 4 Hz, 2H), 1.99 (m, 2H).

INTERMEDIATE 5



3-(4-Piperidinyl)quinolin-2-(1*H*)-one

Step A. 3-(1-Benzyl-4-hydroxypiperidin-4-yl)-2-chloroquinoline

A solution of n-butyllithium in hexane (1.6 M, 38.2 mL, 61.1 mmol) was added to a solution of diisopropylamine (8.6 mL, 61.1 mmol) in tetrahydrofuran (140 mL) at –78°C under argon. After 1 h, a solution of 2-chloroquinoline (10.00 g, 61.1 mol) in tetrahydrofuran (30 mL) was added via syringe. After 1 h, a solution of 1-benzyl-4-piperdinone (11.3 mL, 61.1 mmol) was added, and the reaction stirred for an additional 40 min at –78°C, then allowed to warm to room temperature. The reaction was cooled to –20°C and quenched with water. The reaction solution was extracted with ethyl acetate, and the organic phase washed with saturated brine and dried over magnesium sulfate. Chromatographic purification (silica gel,0 to 10% {5% ammonium hydroxide/methanol} in methylene chloride gradient elution) gave the title compound, 11.3 g. MS 353 (M+1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.33 (s, 1H), 8.00 (d, J = 8 Hz, 1H), 7.82 (d, J = 8 Hz, 1H), 7.72 (dt, J = 1,10 Hz, 1H), 7.57 (dt, J = 1,8 Hz, 1H), 7.39-7.26 (m, 5H), 3.61 (s, 2H), 2.85 (d, J = 11 Hz, 2H), 2.59 (t, J = 12 Hz, 2H), 2.48 (dt, J = 4,13 Hz, 2H), 2.13 (d, J = 12 Hz, 2H).

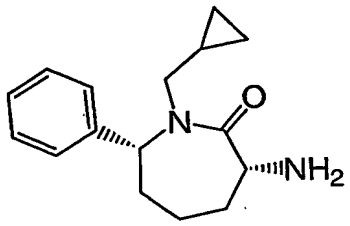
Step B. 3-(1-Benzyl-1,2,3,6-tetrahydropyridin-4-yl)quinolin-2-(1*H*)-one

3-(1-Benzyl-4-hydroxypiperidin-4-yl)-2-chloroquinoline (11.0 g, 31.1 mmol) was refluxed in 6 N hydrochloric acid for 8 h. The solution was cooled and water (100 mL) added. The precipitated solid was collected and dried to give the title compound, 7.9 g. MS 317 (M+1). ^{1}H NMR (500 MHz, CD_3OD) δ 7.97 (s, 1H), 7.70 (d, J = 7 Hz, 1H), 7.60 (m, 2H), 7.55 (m, 4H), 7.35 (d, J = 9 Hz, 1H), 7.27 (t, J = 8 Hz, 1H), 6.50 (m, 1H), 4.49 (ABq, J = 13 Hz, Δν= 16 Hz, 2H), 3.92 (m, 2H), 3.76 (dt, J = 12,4 Hz, 1H), 3.40 (m, 1H), 2.96 (m, 2H).

Step C. 3-(4-Piperidinyl)quinolin-2-(1*H*)-one

A solution of 3-(1-benzyl-1,2,3,6-tetrahydropyridin-4-yl)quinolin-2-(1*H*)-one (4.00 g, 12.6 mmol) in methanol (500 mL) was degassed with argon, and 10% palladium on carbon (1.2 g) added. The reaction was placed under 1 atm hydrogen and heated to 50°C for 5.5 h. The reaction was cooled and filtered through celite. Concentration provided the title compound, 2.7 g. MS 229 (M+1). ^{1}H NMR (500 MHz, CD_3OD) δ 7.80 (s, 1H), 7.67 (d, J = 8 Hz, 1H), 7.51 (t, J = 8 Hz, 1H), 7.33 (d, J = 8 Hz, 1H), 7.25 (t, J = 8 Hz, 1H), 3.52 (t, J = 12 Hz, 2H), 3.17 (dt, J = 3, 13 Hz, 2H), 3.15 (m, overlaps with δ 3.17 peak, 1H), 2.18 (d, J = 14 Hz, 2H), 1.91 (dq, J = 3, 12 Hz, 2H).

INTERMEDIATE 6



(3*R*,7*R*)-3-Amino-1-(cyclopropylmethyl)-7-phenylazepan-2-one

Step A: 3-Bromo-7-phenylazepan-2-one

Phosphorus pentachloride (4.95 g, 23.8 mmol) was added to a solution of 7-phenylazepan-2-one (4.50 g, 23.8 mmol) in dichloromethane (75 mL) at 0 °C. After 1 h, iodine (0.060 g, 0.24 mmol) and a solution of bromine (1.22 mL, 23.8 mmol) in dichloromethane (10 mL) were added sequentially and the mixture was allowed to warm to ambient temperature. After 1.5 h, the reaction was quenched with aqueous sodium sulfite. The mixture was extracted

with dichloromethane (3x), and the combined organic extracts were dried over magnesium sulfate, filtered, and concentrated. Purification by silica gel chromatography (10% ethyl acetate/ hexanes → 50% ethyl acetate/ hexanes) gave the title compound (4.91 g). MS 268 (M+1).

Step B: (3*R*,7*R*)-3-Azido-7-phenylazepan-2-one

Sodium azide (8.73 g, 134 mmol) was added to a solution of 3-bromo-7-phenylazepan-2-one in *N*,*N*-dimethylformamide (40 mL) and the mixture heated to 60 °C. After 2 h the reaction was allowed to cool to ambient temperature, concentrated, and diluted with water. The mixture was extracted with ethyl acetate, and the organic layer was washed with water (3x) and saturated brine, dried over magnesium sulfate, filtered, and concentrated. Purification by silica gel chromatography (30% ethyl acetate/ hexanes → 50% ethyl acetate/ hexanes) gave the racemic cis and trans compounds. The cis enantiomers were separated on a Chiralpak AD column eluting with 100% methanol to give the title compound (1.09 g). MS 231 (M+1).

Step C: *tert*-Butyl (3*R*,7*R*)-2-oxo-7-phenylazepan-3-ylcarbamate

10% palladium on carbon (0.90 g) was added to a solution (3*R*,7*R*)-3-azido-7-phenylazepan-2-one (0.89 g, 3.87 mmol) in ethanol (10 mL). The reaction vessel was evacuated and back-filled with nitrogen (3x), then back-filled with hydrogen (1 atm). After 18 h, the mixture was filtered and concentrated. Triethylamine (0.61 mL, 4.41 mmol) was added to a solution of the crude amine and di-*tert*-butyl dicarbonate (0.96 g, 4.41 mmol) in dichloromethane (20 mL). After 1 h, the mixture was concentrated. Purification by silica gel chromatography (100% dichloromethane → 95% dichloromethane/ methanol) gave the title compound (0.79 g).

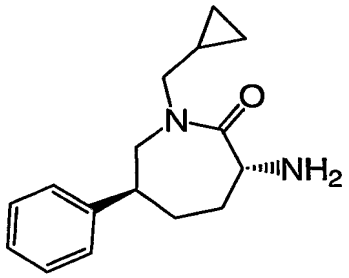
Step D: *tert*-Butyl (3*R*,7*R*)-1-(cyclopropylmethyl)-2-oxo-7-phenylazepan-3-ylcarbamate

Sodium hydride (60% dispersion in mineral oil; 14.4 mg, 0.36 mmol) was added to a solution of *tert*-butyl (3*R*,7*R*)-2-oxo-7-phenylazepan-3-ylcarbamate (100 mg, 0.33 mmol) and cyclopropylmethyl bromide (0.08 mL, 0.82 mmol) in *N*,*N*-dimethylformamide (1 mL) at 0 °C, and the mixture was allowed to warm to ambient temperature. After 6 h, the reaction was quenched with water and the mixture was extracted with ethyl acetate. The organic layer was washed with water (3x), saturated brine, dried over magnesium sulfate, filtered and concentrated. Purification by silica gel chromatography (10% ethyl acetate/ hexanes → 50% ethyl acetate/ hexanes) gave the title compound (82 mg). MS 359 (M+1).

Step E: (3*R*,7*R*)-3-Amino-1-(cyclopropylmethyl)-7-phenylazepan-2-one

Trifluoroacetic acid (2.5 mL) was added to a solution *tert*-butyl (3*R*,7*R*)-1-(cyclopropylmethyl)-2-oxo-7-phenylazepan-3-ylcarbamate (82 mg, 0.23 mmol) in dichloromethane (5 mL). After 1 h, the mixture was concentrated and aqueous saturated sodium bicarbonate was added. The mixture was extracted with dichlormethane (2x), and the combined organic extracts were dried over magnesium sulfate, filtered, and concentrated to give the title compound (53 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40-7.37 (m, 2H), 7.34-7.31 (m, 3H), 4.97 (dd, J = 9.3, 3.7 Hz, 1H), 4.05 (dd, J = 9.8, 4.2 Hz, 1H), 3.24 (dd, J = 14.4, 7.1 Hz, 1H), 2.69 (dd, J = 14.2, 7.1 Hz, 1H), 2.16-2.10 (m, 2H), 2.03-1.97 (m, 1H), 1.92-1.85 (m, 2H), 1.65-1.56 (m, 1H), 0.69-0.63 (m, 1H), 0.34-0.23 (m, 2H), 0.09-0.04 (m, 1H), -0.10--0.15 (m, 1H).

INTERMEDIATE 7



(3*R*,6*S*)-3-Amino-1-(cyclopropylmethyl)-6-phenylazepan-2-one

Step A: 1-(Cyclopropylmethyl)-6-phenylazepan-2-one

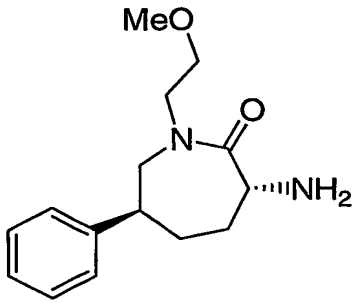
Sodium hydride (60% dispersion in mineral oil; 0.793 g, 19.8 mmol) was added to a solution of 6-phenylazepan-2-one (2.50g, 13.2 mmol) and cyclopropylmethyl bromide (1.92 mL, 19.8 mmol) in *N*,*N*-dimethylformamide (30 mL) at 0 °C, then the mixture allowed to warm to ambient temperature. After 18 h the mixture was quenched with water and extracted with ethyl acetate. The organic layer was washed with water (3x) and saturated brine, dried over magnesium sulfate, filtered, and concentrated. Purification by silica gel chromatography (1% methanol/ dichloromethane → 5% methanol/ dichloromethane) gave the title compound (2.33 g). MS 244 (M+1).

Step B: (3*R*,6*S*)-3-Amino-1-(cyclopropylmethyl)-6-phenylazepan-2-one

Phosphorus pentachloride (1.99 g, 9.57 mmol) was added to a solution of 1-(cyclopropylmethyl)-6-phenylazepan-2-one (2.33 g, 9.57 mmol) in dichloromethane (55 mL) at 0

°C. After 1 h, iodine (0.024 g, 0.096 mmol) and a solution of bromine (0.49 mL, 9.57 mmol) in dichloromethane (5 mL) were added sequentially and the mixture was allowed to warm to ambient temperature. After 18 h, the reaction was quenched with aqueous sodium sulfite. The mixture was extracted with dichloromethane (3x), and the combined organic extracts were dried over magnesium sulfate, filtered, and concentrated. Sodium azide (5.60 g, 86.2 mmol) was added to a solution of the crude bromide in *N,N*-dimethylformamide (50 mL) and the mixture heated to 50° C. After 4 h, the reaction was allowed to cool to ambient temperature, concentrated, and diluted with water. The mixture was extracted with ethyl acetate, washed with water (3x) and saturated brine, dried over magnesium sulfate, filtered, and concentrated. 10% palladium on carbon (0.50 g) was added to a solution of the crude azide in ethanol (50 mL). The reaction vessel was evacuated and back-filled with nitrogen (3x), then back-filled with hydrogen (1 atm). After 18 h, the mixture was filtered and concentrated. Purification by silica gel chromatography [100% dichloromethane → 95% dichloromethane/ (10% ammonium hydroxide/ methanol)] gave the racemic amine. The cis and trans enantiomers were both separated using a Chiralcel OD column eluting with 5% 2-propanol/ 90% (hexanes with 0.1% diethyl amine)/ 5% methanol to give the title compound (247 mg). MS 259 (M+1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (t, J = 7.6 Hz, 2H), 7.26-7.23 (m, 1H), 7.17 (d, J = 7.6 Hz, 2H), 3.86-3.81 (m, 2H), 3.62 (dd, J = 13.9, 6.8 Hz, 1H), 3.32 (d, J = 11.1 Hz, 1H), 3.08 (dd, J = 13.9, 7.3 Hz, 1H), 2.79-2.74 (m, 1H), 2.14-2.12 (m, 1H), 2.02-1.97 (m, 2H), 1.77-1.67 (m, 1H), 1.03-0.99 (m, 1H), 0.55-0.49 (m, 2H), 0.28-0.25 (m, 2H).

INTERMEDIATE 8



(3*R*,6*S*)-3-Amino-1-(2-methoxyethyl)-6-phenylazepan-2-one

Step A: 2-Bromo-*N*-(2,4-dimethoxybenzyl)prop-2-en-1-amine

Triethylamine (16.0 mL, 114 mmol) was added to a solution of 2,4-dimethoxybenzylamine hydrochloride (11.1 g, 54.5 mmol) and 2,3-dibromopropene (10.9 g, 54.5 mmol) in dichloromethane (200 mL). After 18 h, water was added and the mixture was extracted with dichloromethane (3x). The combined organic extracts were washed with saturated brine, dried over magnesium sulfate, filtered and concentrated. Purification by silica gel chromatography [100% dichloromethane → 95% dichloromethane/ 5% (10% ammonium hydroxide/ methanol)] gave the title compound (7.85 g).

Step B: Benzyl (1*R*)-1-{[(2-bromoprop-2-enyl)(2,4-dimethoxybenzyl) amino]carbonyl}but-3-enylcarbamate

1-[3-(Dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (55 mg, 0.285 mmol) was added to a solution of 2-bromo-*N*-(2,4-dimethoxybenzyl)prop-2-en-1-amine (73 mg, 0.256 mmol) and (2*R*)-2-{[(benzyloxy)carbonyl]amino}pent-4-enoic acid (71 mg, 0.285 mmol) in dichloromethane (5 mL). After 18 h the mixture was concentrated. Purification by silica gel chromatography (5% ethyl acetate/ hexanes → 30% ethyl acetate/ hexanes) gave the title compound (77 mg). MS 517 (M+1).

Step C: Benzyl (1*R*)-1-{[(2,4-dimethoxybenzyl)(2-phenylprop-2-enyl)amino]carbonyl}but-3-enylcarbamate

Tetrakis(triphenylphosphine)palladium(0) (1.11 g, 0.962 mmol) was added to a solution of benzyl (1*R*)-1-{[(2-bromoprop-2-enyl)(2,4-dimethoxybenzyl) amino]carbonyl}but-3-enylcarbamate (2.49 g, 4.81 mmol), phenylboronic acid (0.65 g, 5.29 mmol) and sodium carbonate (2M in water; 4.81 mL, 9.63 mmol) in tetrahydrofuran (54 mL) and water (20 mL), and the mixture heated to 60 °C. After 1 h, the mixture was allowed to cool to ambient temperature and extracted with dichloromethane (3x). The combined organic extracts were washed with saturated brine, dried over magnesium sulfate, filtered and concentrated. Purification by silica gel chromatography (5% ethyl acetate/ hexanes → 30% ethyl acetate/ hexanes) gave the title compound (2.02 g). MS 515 (M+1).

Step D: Benzyl (3*R*)-1-(2,4-dimethoxybenzyl)-2-oxo-6-phenyl-2,3,4,7-tetrahydro-1H-azepin-3-ylcarbamate

[1,3-Bis-(2,4,6-trimethylphenyl-2-imidazolidinylidene)dichloro(phenylmethylene)-(tricyclohexylphosphine)ruthenium] (Grubbs second generation catalyst) (0.68 g, 0.79 mmol) was added to a solution of benzyl (1*R*)-1-{[(2,4-

dimethoxybenzyl)(2-phenylprop-2-enyl)amino]carbonyl}but-3-enylcarbamate (2.02 g, 3.93 mmol) in dichloromethane (395 mL) and heated to 40 °C. After 40 h, the mixture was allowed to cool to ambient temperature and concentrated. Purification by silica gel chromatography (5% ethyl acetate/ hexanes → 30% ethyl acetate/ hexanes) gave the title compound (1.00 g). MS 487 (M+1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39-7.31 (m, 5H), 7.26-7.19 (m, 3H), 7.17 (d, J = 8.3 Hz, 1H), 6.99 (d, J = 7.1 Hz, 2H), 6.41 (dd, J = 8.3, 2.0 Hz, 1H), 6.33 (s, 1H), 6.22 (d, J = 6.4 Hz, 1H), 5.77-5.76 (m, 1H), 5.16-5.09 (m, 3H), 4.82 (d, J = 14.7 Hz, 1H), 4.65 (dd, J = 17.6, 2.7 Hz, 1H), 4.54 (d, J = 14.4 Hz, 1H), 3.93 (d, J = 17.6 Hz, 1H), 3.77 (s, 3H), 3.64 (s, 3H), 2.91-2.86 (m, 1H), 2.42-2.36 (m, 1H).

Step E: Benzyl (3*R*)-2-oxo-6-phenyl-2,3,4,7-tetrahydro-1H-azepin-3-ylcarbamate

A solution of L-methionine (2.56 g, 17.2 mmol) in trifluoroacetic acid (15 mL) was added to a solution of benzyl (3*R*)-1-(2,4-dimethoxybenzyl)-2-oxo-6-phenyl-2,3,4,7-tetrahydro-1H-azepin-3-ylcarbamate (0.84 g, 1.72 mmol) in dichloromethane (20 mL). After 18 h, the mixture was concentrated and water was added. The mixture was extracted with ethyl acetate, washed with water (2x), saturated aqueous sodium bicarbonate (2x), saturated brine, dried over magnesium sulfate, filtered and concentrated. Purification by silica gel chromatography (5% ethyl acetate/ hexanes → 50% ethyl acetate/ hexanes) gave the title compound (0.44 g). MS 337 (M+1).

Step F: *tert*-Butyl (3*R*,6*S*)-2-oxo-6-phenylazepan-3-ylcarbamate

10% palladium on carbon (75 mg) was added to a solution of benzyl (3*R*)-2-oxo-6-phenyl-2,3,4,7-tetrahydro-1H-azepin-3-ylcarbamate (596 mg, 1.77 mmol) and di-*tert*-butyl dicarbonate (773 mg, 3.54 mmol) in ethyl acetate (30 mL). The reaction vessel is evacuated and back-filled with nitrogen (3x), then back-filled with hydrogen (1 atm). After 2 h, the mixture was filtered and concentrated. Purification by silica gel chromatography (30% ethyl acetate/ hexanes → 50% ethyl acetate/ hexanes) gave the title compound (289 mg).

Step G: *tert*-Butyl (3*R*,6*S*)-1-(2-methoxyethyl)-2-oxo-6-phenylazepan-3-ylcarbamate

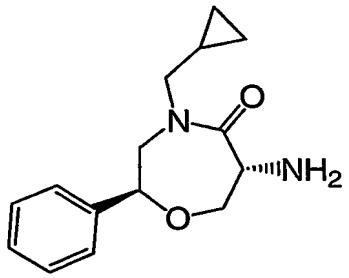
Sodium hydride (60% dispersion in mineral oil; 6.2 mg, 0.158 mmol) was added to a solution of *tert*-butyl (3*R*,6*R*)-2-oxo-6-phenylazepan-3-ylcarbamate (40 mg, 0.131 mmol) and 2-bromoethyl methyl ether (0.013 mL, 0.138 mmol) in *N*,*N*-dimethylformamide (2 mL) at 0 °C. After addition, the mixture was allowed to warm to ambient temperature. After 4 h, the reaction was quenched with water and the mixture was extracted with ethyl acetate. The organic

layer was washed with water (3x), saturated brine, dried over magnesium sulfate, filtered and concentrated. Purification by silica gel chromatography (5% ethyl acetate/ hexanes → 30% ethyl acetate/ hexanes) gave the title compound (41 mg). MS 363 (M+1).

Step H: (3*R*,6*S*)-3-Amino-1-(2-methoxyethyl)-6-phenylazepan-2-one

Trifluoroacetic acid (2.5 mL) was added to a solution of *tert*-butyl (3*R*,6*S*)-1-(2-methoxyethyl)-2-oxo-6-phenylazepan-3-ylcarbamate (41 mg, 0.113 mmol) in dichloromethane (5 mL). After 1 h, the solution was concentrated. Saturated aqueous sodium bicarbonate solution was added and the mixture was extracted with dichloromethane (3x). The combined organic extracts were washed with saturated brine, dried over magnesium sulfate, filtered and concentrated. MS 263 (M+1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (t, J = 7.3 Hz, 2H), 7.25-7.22 (m, 1H), 7.18 (d, J = 8.3 Hz, 2H), 3.83-3.76 (m, 3H), 3.56-3.49 (m, 3H), 3.35 (s, 3H), 3.34-3.30 (m, 1H), 2.77-2.72 (m, 1H), 2.13-2.10 (m, 1H), 2.03-1.94 (m, 2H), 1.74-1.68 (m, 1H).

INTERMEDIATE 9



(2*S*,6*R*)-6-Amino-4-(cyclopropylmethyl)-2-phenyl-1,4-oxazepan-5-one

Step A: *tert*-Butyl cyclopropylmethyl[(2*S*)-2-hydroxy-2-phenylethyl]carbamate

(*S*)-styrene oxide (4.83 g, 40.3 mmol) and cyclopropanemethylamine (4.00 g, 56.4 mmol) were dissolved in isopropyl alcohol (100 mL) and heated to reflux. After 8 h, the reaction was allowed to cool to ambient temperature and concentrated. Triethylamine (5.61 mL, 40.3 mmol) was added to a solution of the crude amine and di-*tert*-butyl dicarbonate (8.78 g, 40.3 mmol) in dichloromethane (100 mL). After 18 h, water was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate, filtered and concentrated. Purification by silica gel chromatography (5% ethyl acetate/ hexanes → 20% ethyl acetate/ hexanes) gave the title compound (5.48 g).

Step B: Methyl *N*-[(benzyloxy)carbonyl]-*O*-{(1*S*)-2-[(tert-butoxycarbonyl)(cyclopropylmethyl)amino]-1-phenylethyl}-D-serinate

Boron trifluoride diethyl etherate (0.10 mL, 0.84 mmol) was added to a solution of *tert*-butyl cyclopropylmethyl[(2*S*)-2-hydroxy-2-phenylethyl]carbamate (2.45 g, 8.39 mmol) and 1-benzyl 2-methyl (2*R*)-aziridine-1,2-dicarboxylate (1.97 g, 8.39 mmol) in chloroform (20 mL). After 3 h, the reaction was concentrated. Purification by silica gel chromatography (100% hexanes → 30% ethyl acetate/ hexanes) gave the title compound (1.21 g).

Step C: *N*-[(Benzyloxy)carbonyl]-*O*-{(1S)-2-[(tert-butoxycarbonyl) (cyclopropylmethyl)amino]-1-phenylethyl}-D-serine

Aqueous sodium hydroxide (1N; 3.81 mL, 3.81 mmol) was added to a solution of methyl *N*-[(benzyloxy)carbonyl]-*O*-{(1S)-2-[(tert-butoxycarbonyl)(cyclopropylmethyl)amino]-1-phenylethyl}-D-serinate (1.30 g, 2.46 mmol) in tetrahydrofuran (20 mL). After 18 h, aqueous hydrochloric acid (1N; 3.81 mL, 3.81 mmol) was added. The mixture was extracted with dichloromethane (3x), and the combined organic extracts were dried over magnesium sulfate, filtered, and concentrated to give the title compound. (1.27 g) MS 535 (M+Na).

Step D: Benzyl (2*S*,6*R*)-4-(cyclopropylmethyl)-5-oxo-2-phenyl-1,4-oxazepan-6-ylcarbamate

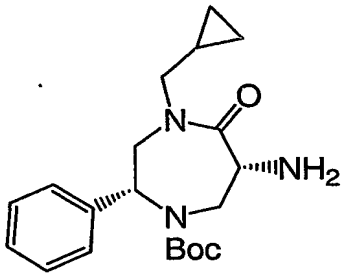
Trifluoroacetic acid (5.0 mL) was added to a solution *N*-[(benzyloxy)carbonyl]-*O*-{(1*S*)-2-[(tert-butoxycarbonyl) (cyclopropylmethyl)amino]-1-phenylethyl}-D-serine (1.27 g, 2.47 mmol) in dichloromethane (15 mL). After 2 h, the mixture was concentrated and azeotroped with toluene (3x) to give the crude amine. Diphenylphosphoryl azide (1.07 ml, 4.95 mmol) was added to a solution of the crude amine and 4-methylmorpholine (0.82 mL, 7.41 mmol) in *N*,*N*-dimethylformamide (100 mL). After 18 h, the mixture was concentrated and water was added. The mixture was extracted with ethyl acetate, and the organic layer was washed with water (2x) and saturated brine, dried over magnesium sulfate, filtered, and concentrated. Purification by silica gel chromatography (5% ethyl acetate/ hexanes → 50% ethyl acetate/ hexanes) gave the title compound (0.426 g). MS 395 (M+1).

Step E: (2*S*,6*R*)-6-Amino-4-(cyclopropylmethyl)-2-phenyl-1,4-oxazepan-5-one

10% palladium on carbon (20 mg) was added to a solution (2*S*,6*R*)-6-amino-4-(cyclopropylmethyl)-2-phenyl-1,4-oxazepan-5-one (179 mg, 0.454 mmol) in ethanol (15 mL). The reaction vessel was evacuated and back-filled with nitrogen (3x), then back-filled with hydrogen (1 atm). After 18 h, the mixture was filtered and concentrated to give the title

compound (113 mg). MS 261 (M+1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40-7.31 (m, 5H), 4.53 (d, J = 8.5 Hz, 1H), 4.10-4.03 (m, 2H), 3.90 (dd, J = 15.9, 7.1 Hz, 1H), 3.80-3.65 (m, 2H), 3.36 (d, J = 15.9 Hz, 1H), 3.03 (dd, J = 13.9, 6.6 Hz, 1H), 1.06-1.01 (m, 1H), 0.64-0.53 (m, 2H), 0.33-0.25 (m, 2H).

INTERMEDIATE 10



cis tert-Butyl (2*R*,6*R* and 2*S*,6*S*)-6-amino-4-(cyclopropylmethyl)-5-oxo-2-phenyl-1,4-diazepane-1-carboxylate

Step A. Ethyl 3-[(2-amino-1-phenylethyl)amino]propanoate

trans-β-Nitrostyrene (4.04 g, 27.1 mmol) was added to a solution of ethyl 3-aminopropanoate hydrochloride (4.16 g, 27.1 mmol), and *N*,*N*-diisopropylethylamine (9.43 mL, 54.2 mmol) in acetonitrile (70 mL). After 15 min, anhydrous hydrochloric acid gas was bubbled into the solution until acidic. The mixture was concentrated, redissolved in ethanol (60 mL) and aqueous hydrochloric acid (12M; 30 mL), and cooled to 0 °C. Zinc dust (8.80 g, 134 mmol) was added in portions over 5 min. After 0.5 h, the mixture was concentrated to remove ethanol and saturated aqueous sodium carbonate was added. The mixture was extracted with dichloromethane (3x), and the combined organic extracts were dried over magnesium sulfate, filtered and concentrated to give the title compound (9.5 g). MS 237 (M+1).

Step B. Ethyl N-{2-[(cyclopropylmethyl)amino]-1-phenylethyl}-beta-alaninate

A mixture of ethyl 3-[(2-amino-1-phenylethyl)amino]propanoate (6.38 g, 27.0 mmol), magnesium sulfate (10 g, 83.1 mmol), and cyclopropanecarboxaldehyde (2.02 mL, 27.2 mmol) in dichloroethane (200 mL) was adjusted to pH 6 with acetic acid. After 1 h, sodium triacetoxyborohydride (5.72 g, 27.0 mmol) was added. After an additional 30 min, saturated aqueous sodium bicarbonate was added and the mixture was extracted with dichloromethane (3x). The combined organic extracts were dried over magnesium sulfate, filtered, and

concentrated. Purification by silica gel chromatography [100% dichloromethane → 95% dichloromethane/ 5% (10% ammonium hydroxide/ methanol)] gave the title compound (3.14 g). MS 291 (M+1).

Step C. 4-(Cyclopropylmethyl)-2-phenyl-1,4-diazepan-5-one

Sodium hydroxide (1M; 6.53 mL, 6.53 mmol) was added to a solution of ethyl *N*-{2-[(cyclopropylmethyl)amino]-1-phenylethyl}-beta-alaninate (1.81 g, 6.22 mmol) in methanol (10 mL). After 1 h, the mixture was concentrated and azeotroped with toluene (3x) to give the crude acid. Diphenylphosphoryl azide (2.68 ml, 12.43 mmol) was added to a solution of the crude acid (1.77 g, 6.22 mmol) and 4-methylmorpholine (1.37 mL, 12.4 mmol) in *N*,*N*-dimethylformamide (124 mL). After 18 h, the reaction was concentrated and diluted with water. The mixture was extracted with dichloromethane (3x), and the combined organic extracts were dried over magnesium sulfate, filtered, and concentrated. Purification by silica gel chromatography [100% dichloromethane → 90% dichloromethane/ 10% (10% ammonium hydroxide/ methanol)] gave the title compound (1.38 g). MS 245 (M+1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47-7.30 (m, 5H), 3.89-3.88 (m, 2H), 3.65 (dd, J = 13.9, 6.6 Hz, 1H), 3.31-3.26 (m, 1H), 3.24-3.21 (m, 1H), 3.02-2.93 (m, 3H), 2.70-2.65 (m, 1H), 1.02-0.97 (m, 1H), 0.58-0.49 (m, 2H), 0.28-0.21 (m, 2H).

Step D. *tert*-Butyl 4-(cyclopropylmethyl)-5-oxo-2-phenyl-1,4-diazepane-1-carboxylate

Triethylamine (0.53 mL, 3.79 mmol) was added to a solution of 4-(cyclopropylmethyl)-2-phenyl-1,4-diazepan-5-one (0.925 g, 3.79 mmol) and di-*tert*-butyl dicarbonate (0.826 g, 3.79 mmol) in dichloromethane (20 mL). After 18 h, the mixture was diluted with water. The mixture was extracted with dichloromethane, washed with saturated brine, dried over magnesium sulfate, filtered, and concentrated. Purification by silica gel chromatography (100% dichloromethane → 95% dichloromethane/ methanol) to give the title compound (1.38 g). MS 345 (M+1).

Step E. *tert*-Butyl 6-bromo-4-(cyclopropylmethyl)-5-oxo-2-phenyl-1,4-diazepane-1-carboxylate

Lithium diisopropylamide (1M in THF; 2.13 mL, 2.13 mmol) was added to *tert*-butyl 4-(cyclopropylmethyl)-5-oxo-2-phenyl-1,4-diazepane-1-carboxylate (0.489 g, 1.42 mmol) in tetrahydrofuran (5 mL) at –78 °C. After 30 min, the enolate solution was transferred dropwise *via cannula* to a solution of bromine (0.36 mL, 7.10 mmol) in tetrahydrofuran (3 mL) at –78 °C over a period of 5 min. After 15 min, the mixture was quenched with aqueous saturated sodium

sulfite and allowed to warm to ambient temperature. The mixture was extracted with ethyl acetate, washed with saturated aqueous sodium bicarbonate and saturated brine, dried over magnesium sulfate, filtered, and concentrated. MS 423 (M+1).

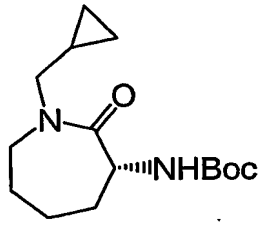
Step F. cis and trans *tert*-Butyl-6-azido-4-(cyclopropylmethyl)-5-oxo-2-phenyl-1,4-diazepane-1-carboxylate

Sodium azide (0.841 g, 12.9 mmol) was added to a solution of *tert*-butyl 6-bromo-4-(cyclopropylmethyl)-5-oxo-2-phenyl-1,4-diazepane-1-carboxylate (0.609 g, 1.43 mmol) in *N*,*N*-dimethylforamide (10 mL) and heated to 70 °C. After 1 h, the mixture was allowed to cool to ambient temperature and water was added. The mixture was extracted with ethyl acetate, washed with water (3x), saturated brine, dried over magnesium sulfate, filtered, and concentrated. Purification by silica gel chromatography (20% ethyl acetate/ hexanes → 50% ethyl acetate/ hexanes) gave 170 mg of the trans isomer and 30 mg of the cis isomer. MS 386 (M+1).

Step G: Cis *tert*-Butyl (2*R*,6*R* and 2*S*,6*S*)-6-amino-4-(cyclopropylmethyl)-5-oxo-2-phenyl-1,4-diazepane-1-carboxylate

10% Palladium on carbon (20 mg) was added to a solution of cis *tert*-butyl-6-azido-4-(cyclopropylmethyl)-5-oxo-2-phenyl-1,4-diazepane-1-carboxylate (165 mg, 0.428 mmol) in ethanol (15 mL). The reaction vessel was evacuated and back-filled with nitrogen (3x), then back-filled with hydrogen (1 atm). After 2 h, the mixture was filtered and concentrated to give the title compound (20 mg).

INTERMEDIATE 11

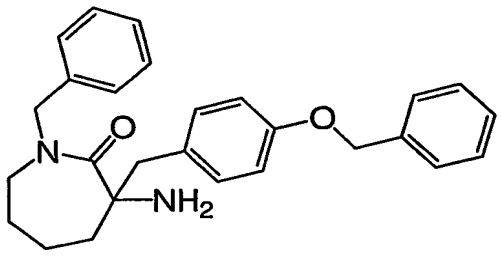


tert-Butyl (3*R*)-1-(cyclopropylmethyl)-2-oxoazepan-3-ylcarbamate

Sodium hydride (60% dispersion in mineral oil; 30 mg, 1.24 mmol) was added to a solution *tert*-butyl (3*R*)-2-oxoazepan-3-ylcarbamate (258 mg, 1.13 mmol) and

cyclopropylmethyl bromide (0.27 mL, 2.83 mmol) in *N*,*N*-dimethylformamide (3 mL) at 0 °C, and the mixture was allowed to warm to ambient temperature. After 6 h, the reaction was quenched with water and the mixture was extracted with ethyl acetate. The organic layer was washed with water (3x), saturated brine, dried over magnesium sulfate, filtered and concentrated. Purification by silica gel chromatography (100% dichloromethane → 5% methanol/ dichloromethane) gave the title compound (257 mg). MS 283 (M+1).

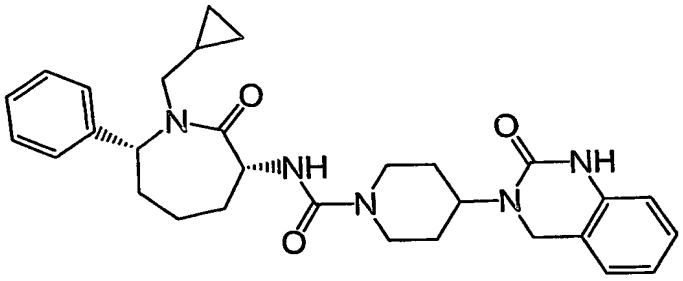
INTERMEDIATE 12



3-Amino-1-benzyl-3-[4-(benzyloxy)benzyl]azepan-2-one

Magnesium sulfate (5.0 g, 41.5 mmol) was added to a solution of commercially available 3-amino-1-benzylazepan-2-one (940 mg, 4.31 mmol), triethylamine (0.60 mL, 4.31 mmol) and benzaldehyde (0.46 mL, 4.52 mmol) in dichloromethane (20 mL). After 18 h, the mixture was filtered and concentrated to give the crude imine. Lithium bis(trimethylsilyl)amide (1M in tetrahydrofuran; 1.42 mL, 1.42 mmol) was added to a solution of the crude imine (363 mg, 1.19 mmol) in tetrahydrofuran (4 mL). After 2 h, the mixture was cooled to 0 °C. 4-benzyloxybenzyl chloride (290 mg, 1.24 mmol) was added and the mixture was allowed to warm to ambient temperature. After an additional 18 h, the mixture was quenched with 1N hydrochloric acid (10 mL). After 30 min, the mixture was extracted with ethyl acetate, and the organic layer was washed with aqueous saturated sodium carbonate, water, saturated brine, dried over magnesium sulfate, filtered, and concentrated. Purification by silica gel chromatography [100% dichloromethane → 90% dichloromethane/ 10% methanol (10% ammonium hydroxide/ methanol)] gave the title compound. (109 mg) MS 415 (M+1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44-7.36 (m, 4H), 7.34-7.23 (m, 6H), 7.03 (d, J = 8.6 Hz, 2H), 6.81 (d, J = 8.6 Hz, 2H), 5.29 (s, 2H), 4.64-4.52 (m, 2H), 3.31-3.26 (m, 1H), 3.22-3.18 (m, 1H), 3.02 (d, J = 13.4 Hz, 1H), 2.86 (d, J = 13.7 Hz, 1H), 1.90-1.75 (m, 4H), 1.72-1.60 (m, 2H), 1.49-1.42 (m, 2H).

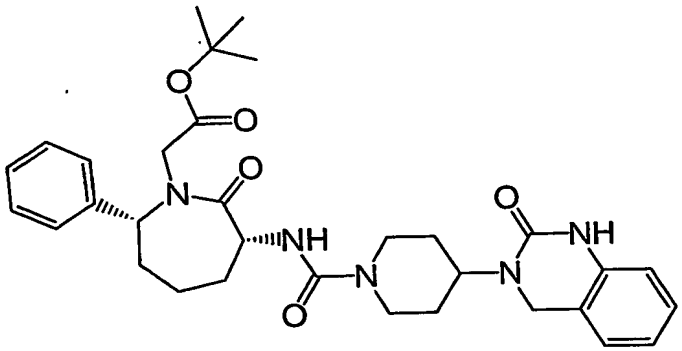
EXAMPLE 1



N-[(3*R*,7*R*)-1-(Cyclopropylmethyl)-2-oxo-7-phenylazepan-3-yl]-4-(2-oxo-1,4-dihydroquinazolin-3(2H)-yl)piperidine-1-carboxamide

Triethylamine (0.010 mL, 0.075 mmol) was added to a solution of (3*R*,7*R*)-3-amino-1-(cyclopropylmethyl)-7-phenylazepan-2-one (26 mg, 0.148 mmol) and 4-nitrophenyl chloroformate (16 mg, 0.080 mmol) in tetrahydrofuran (2 mL) at 0 °C. After 30 min, 4-(2-oxo-1,4-dihydroquinazolin-3(2H)-yl)piperidinium chloride (20 mg, 0.075 mmol), diisopropylethylamine (0.030 mL, 0.19 mmol) and 1,2-dichloroethane (3 mL) were added and the mixture was heated to reflux. After 18 h, the mixture was allowed to cool to ambient temperature and concentrated. Purification by silica gel chromatography (1% methanol/ dichloromethane → 5% methanol/ dichloromethane) gave the title compound (29 mg). MS 516 (M+1).

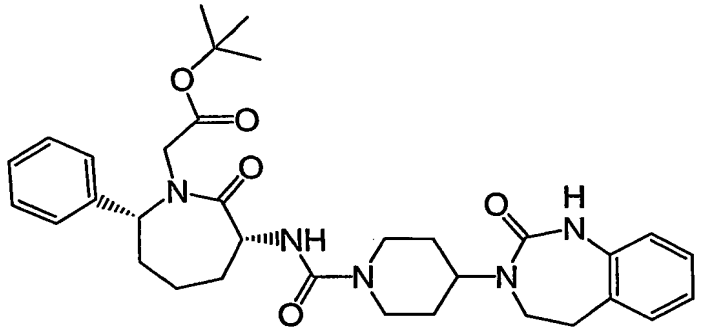
EXAMPLE 2



tert-Butyl [(3*R*,7*R*)-2-oxo-3-({[4-(2-oxo-1,4-dihydroquinazolin-3(2H)-yl)piperidin-1-yl]carbonyl}amino)-7-phenylazepan-1-yl]acetate

The title compound was prepared with *tert*-butyl [(3*R*,7*R*)-3-amino-2-oxo-7-phenylazepan-1-yl]acetate and 4-(2-oxo-1,4-dihydroquinazolin-3(2H)-yl)piperidine-1-carbonyl chloride using a similar procedure to Example 1. MS 576 (M+1).

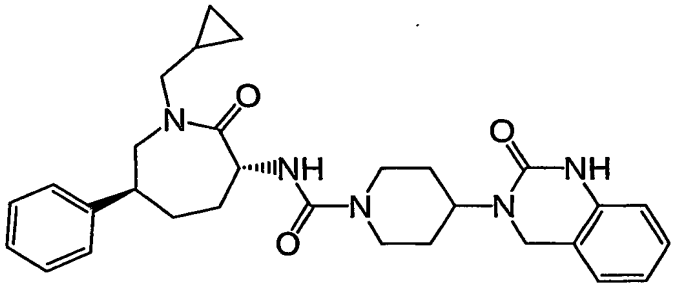
EXAMPLE 3



tert-Butyl [(3*R*,7*R*)-2-oxo-3-({[4-(2-oxo-1,2,4,5-tetrahydro-3H-1,3-benzodiazepin-3-yl)piperidin-1-yl]carbonyl}amino)-7-phenylazepan-1-yl]acetate

The title compound was prepared with *tert*-butyl [(3*R*,7*R*)-3-amino-2-oxo-7-phenylazepan-1-yl]acetate and 4-(2-oxo-1,2,4,5-tetrahydro-3H-1,3-benzodiazepin-3-yl)piperidinium chloride using a similar procedure to Example 1. MS 590.3351 (M+1).

EXAMPLE 4

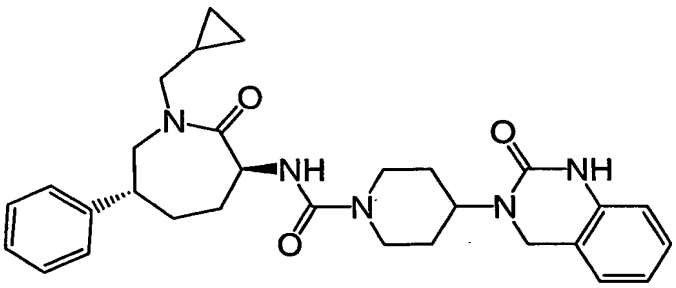


N-[(3*R*,6*S*)-1-(Cyclopropylmethyl)-2-oxo-6-phenylazepan-3-yl]-4-(2-oxo-1,4-dihydroquinazolin-3(2H)-yl)piperidine-1-carboxamide

Diisopropylethylamine (0.16 mL, 0.90 mmol) was added to a solution of (3*R*,6*S*)-3-amino-1-(cyclopropylmethyl)-6-phenylazepan-2-one (116 mg, 0.45 mmol) and 4-(2-oxo-1,4-

dihydroquinazolin-3(2H)-yl)piperidine-1-carbonyl chloride (132 mg, 0.45 mmol) in 1,2-dichloroethane (10 mL) and the mixture heated to reflux. After 1 h, the mixture was allowed to cool to ambient temperature and concentrated. Purification by silica gel chromatography (100% dichloromethane → 5% methanol/ dichloromethane) gave the title compound (32 mg). MS 516 (M+1).

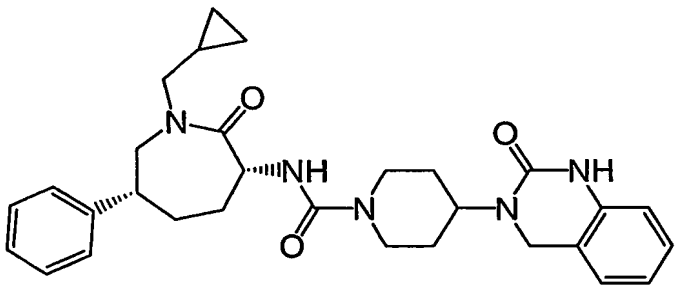
EXAMPLE 5



N-[(3*S*,6*R*)-1-(Cyclopropylmethyl)-2-oxo-6-phenylazepan-3-yl]-4-(2-oxo-1,4-dihydroquinazolin-3(2H)-yl)piperidine-1-carboxamide

The title compound was prepared with (3*S*,6*R*)-3-amino-1-(cyclopropylmethyl)-6-phenylazepan-2-one and 4-(2-oxo-1,4-dihydroquinazolin-3(2H)-yl)piperidine-1-carbonyl chloride using a similar procedure to Example 4. MS 516 (M+1).

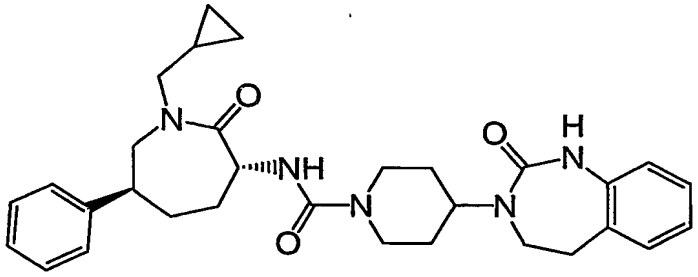
EXAMPLE 6



cis-*N*-1-(Cyclopropylmethyl)-2-oxo-6-phenylazepan-3-yl]-4-(2-oxo-1,4-dihydroquinazolin-3(2H)-yl)piperidine-1-carboxamide

The title compound was prepared with *cis*-3-amino-1-(cyclopropylmethyl)-6-phenylazepan-2-one and 4-(2-oxo-1,4-dihydroquinazolin-3(2H)-yl)piperidine-1-carbonyl chloride using a similar procedure to Example 4. MS 516 (M+1).

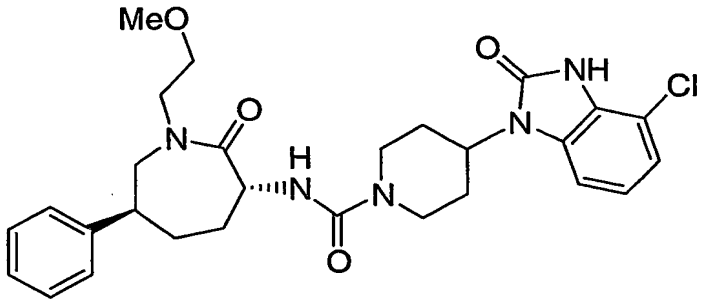
EXAMPLE 7



N-[(3*R*,6*S*)-1-(Cyclopropylmethyl)-2-oxo-6-phenylazepan-3-yl]-4-(2-oxo-1,2,4,5-tetrahydro-3H-1,3-benzodiazepin-3-yl)piperidine-1-carboxamide

The title compound was prepared with (3*R*,6*S*)-3-amino-1-(cyclopropylmethyl)-6-phenylazepan-2-one and 4-(2-oxo-1,2,4,5-tetrahydro-3H-1,3-benzodiazepin-3-yl)piperidinium chloride using a similar procedure to Example 4. MS 530 (M+1).

EXAMPLE 8

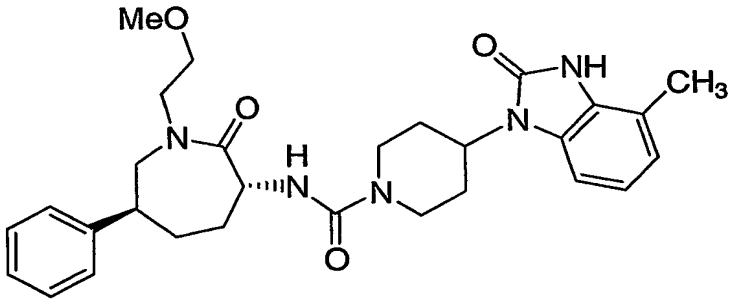


4-(4-Chloro-2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)-*N*-[(3*R*,6*S*)-1-(2-methoxyethyl)-2-oxo-6-phenylazepan-3-yl]piperidine-1-carboxamide

A solution of (3*R*,6*S*)-3-amino-1-(2-methoxyethyl)-6-phenylazepan-2-one (0.015 g, 0.057 mmol) and 4-nitrophenylchloroformate (0.012 g, 0.057 mmol) in dry tetrahydrofuran (2 mL) was cooled to 0°C under argon. Triethylamine (0.006 g, 0.057 mmol) was added and the

reaction stirred for 1 h. Solid 4-chloro-1-piperidin-4-yl-1,3-dihydro-2*H*-benzimidazol-2-one (0.057 mmol) followed by triethylamine (0.055 g) were added. The reaction was allowed to come to room temperature and stirred for 1 h. The reaction was diluted with dicholoromethane and extracted with 1N NaOH until the yellow color of the organic layer disappeared. The organic layer was dried over sodium sulfate, concentrated and purified by normal phase chromatography (silica gel, 0 to 7% methanol in methylene chloride gradient elution), which gave the title compound (9 mg). MS 540.2370 (M+1).

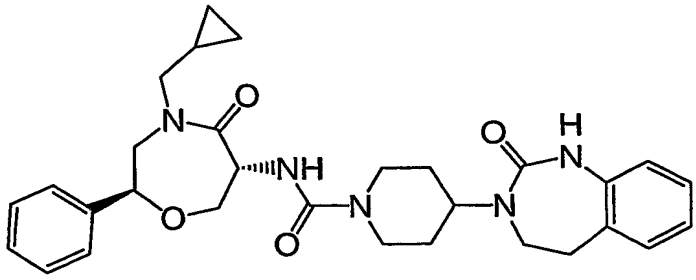
EXAMPLE 9



N-[(3*R*,6*S*)-1-(2-Methoxyethyl)-2-oxo-6-phenylazepan-3-yl]-4-(4-methyl-2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)piperidine-1-carboxamide

The title compound was prepared with (3*R*,6*S*)-3-amino-1-(2-methoxyethyl)-6-phenylazepan-2-one and 4-methyl-1-piperidin-4-yl-1,3-dihydro-2*H*-benzimidazol-2-one using a similar procedure to Example 8. MS 520.2927 (M+1).

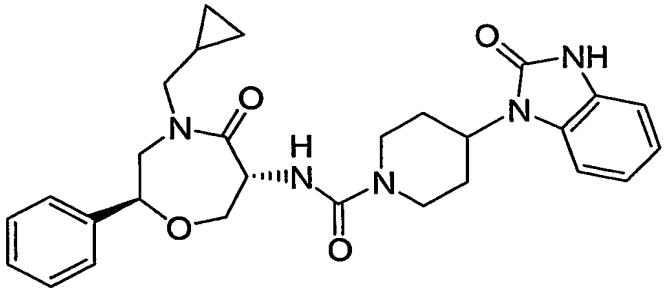
EXAMPLE 10



N-[(2*S*,6*R*)-4-(Cyclopropylmethyl)-5-oxo-2-phenyl-1,4-oxazepan-6-yl]-4-(2-oxo-1,2,4,5-tetrahydro-3H-1,3-benzodiazepin-3-yl)piperidine-1-carboxamide

Triethylamine (0.011 mL, 0.081 mmol) was added to a solution of (2*S*,6*R*)-6-amino-4-(cyclopropylmethyl)-2-phenyl-1,4-oxazepan-5-one (21 mg, 0.081 mmol) and 4-nitrophenyl chloroformate (16 mg, 0.081 mmol) in tetrahydrofuran (1 mL) at 0 °C. After 30 min, diisopropylethylamine (0.042 mL, 0.242 mmol), 4-(2-oxo-1,2,4,5-tetrahydro-3H-1,3-benzodiazepin-3-yl)piperidinium chloride (23 mg, 0.081 mmol), and dichloromethane (1 mL) were added and the mixture heated to 50 °C. After 1 h, the mixture was allowed to cool to ambient temperature and concentrated. Purification by silica gel chromatography (100% dichloromethane → 95% dichloromethane/ methanol) gave the title compound (34 mg). MS 532 (M+1).

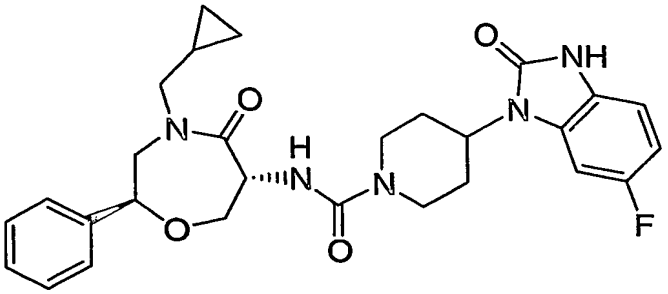
EXAMPLE 11



N-[(2*S*,6*R*)-4-(Cyclopropylmethyl)-5-oxo-2-phenyl-1,4-oxazepan-6-yl]-4-(2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)piperidine-1-carboxamide

The title compound was prepared with (2*S*,6*R*)-6-amino-4-(cyclopropylmethyl)-2-phenyl-1,4-oxazepan-5-one and 1-piperidin-4-yl-1,3-dihydro-2*H*-benzimidazol-2-one using a similar procedure to Example 10. MS 504.2591 (M+1).

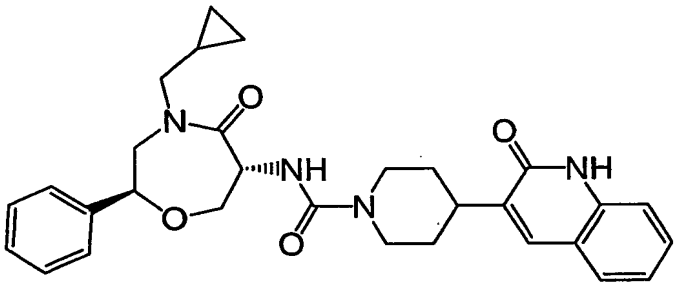
EXAMPLE 12



N-[(2*S*,6*R*)-4-(Cyclopropylmethyl)-5-oxo-2-phenyl-1,4-oxazepan-6-yl]-4-(6-fluoro-2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)piperidine-1-carboxamide

The title compound was prepared with (2*S*,6*R*)-6-amino-4-(cyclopropylmethyl)-2-phenyl-1,4-oxazepan-5-one and 6-fluoro-1-piperidin-4-yl-1,3-dihydro-2*H*-benzimidazol-2-one using a similar procedure to Example 10. MS 522.2521 (M+1).

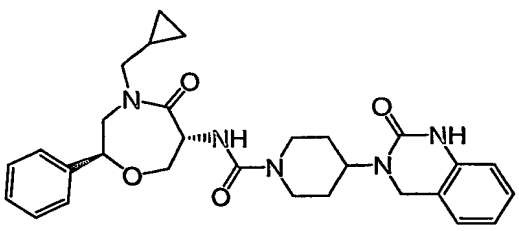
EXAMPLE 13

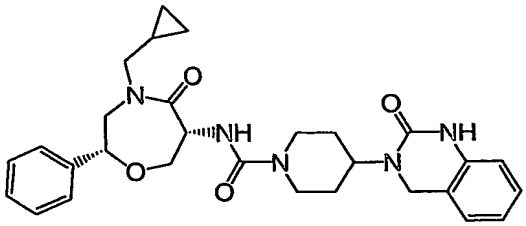


N-[(2*S*,6*R*)-4-(Cyclopropylmethyl)-5-oxo-2-phenyl-1,4-oxazepan-6-yl]-4-(2-oxo-1,2-dihydroquinolin-3-yl)piperidine-1-carboxamide

The title compound was prepared with (2*S*,6*R*)-6-amino-4-(cyclopropylmethyl)-2-phenyl-1,4-oxazepan-5-one and 3-(4-piperidinyl)quinolin-2-(1*H*)-one using a similar procedure to Example 10. MS 515 (M+1).

EXAMPLE 14

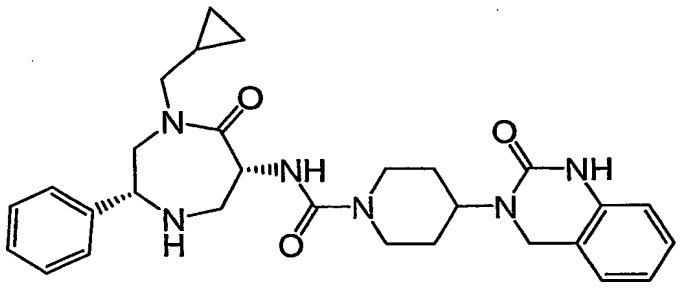




N-[(2*S*,6*R* and 2*R*,6*S*)-4-(Cyclopropylmethyl)-5-oxo-2-phenyl-1,4-oxazepan-6-yl]-4-(2-oxo-1,4-dihydroquinazolin-3(2H)-yl)piperidine-1-carboxamide and *N*-[(2*S*,6*S* and 2*R*,6*R*)-4-(cyclopropylmethyl)-5-oxo-2-phenyl-1,4-oxazepan-6-yl]-4-(2-oxo-1,4-dihydroquinazolin-3(2H)-yl)piperidine-1-carboxamide

The title compounds was prepared using both cis- and trans-6-amino-4-(cyclopropylmethyl)-2-phenyl-1,4-oxazepan-5-one (obtained using racemic styrene oxide and racemic 1-benzyl 2-methyl-aziridine-1,2-dicarboxylate) and 4-(2-oxo-1,4-dihydroquinazolin-3(2H)-yl)piperidine-1-carbonyl chloride using a similar procedure to Example 10. MS 518 (M+1).

EXAMPLE 15

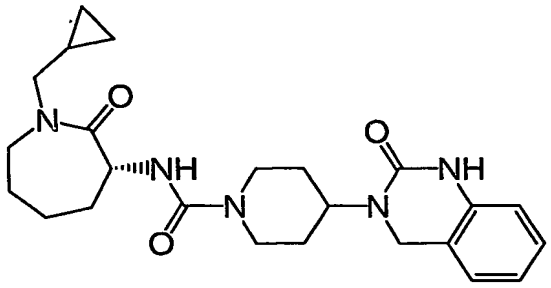


cis *N*-[(3*S*,6*S* and 3*R*,6*R*)-1-(Cyclopropylmethyl)-7-oxo-3-phenyl-1,4-diazepan-6-yl]-4-(2-oxo-1,4-dihydroquinazolin-3(2H)-yl)piperidine-1-carboxamide

Diisopropylethylamine (0.020 mL, 0.11 mmol) was added to a solution of cis *tert*-butyl (2*R*,6*S* and 2*S*,6*R*)-6-amino-4-(cyclopropylmethyl)-5-oxo-2-phenyl-1,4-diazepane-1-carboxylate (20 mg, 0.060 mmol) and 4-(2-oxo-1,4-dihydroquinazolin-3(2H)-yl)piperidine-1-carbonyl chloride (17 mg, 0.060 mmol) in 1,2-dichloroethane (5 mL) and the mixture heated to reflux. After 18 h, the mixture was allowed to cool to ambient temperature and trifluroracetic acid (1 mL) was added. After 1 h, the mixture was concentrated. Purification by reverse phase

HPLC (C-18, 95% water/ acetonitrile → 5% water/ acetonitrile with 0.1% trifluoroacetic acid) gave the title compound (9 mg). MS 517 (M+1).

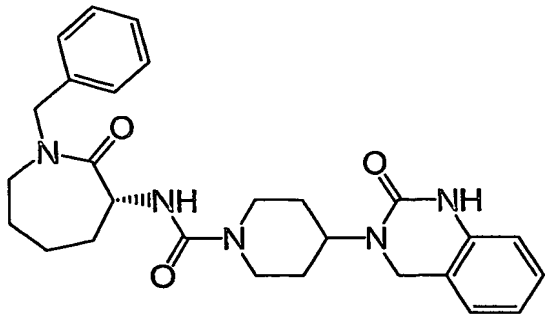
EXAMPLE 16



N-[(3*R*)-1-(Cyclopropylmethyl)-2-oxoazepan-3-yl]-4-(2-oxo-1,4-dihydroquinazolin-3(2H)-yl)piperidine-1-carboxamide

Trifluoroacetic acid (5 mL) was added to a solution of *tert*-butyl (3*R*)-1-(cyclopropylmethyl)-2-oxoazepan-3-ylcarbamate (257 mg, 0.91 mmol) in dichloromethane (10 mL). After 1 h, the mixture was concentrated and azeotroped with dichloromethane (3x) to give the crude amine. Diisopropylethylamine (0.070 mL, 0.40 mmol) was added to a solution of the crude amine (39 mg, 0.13 mmol) and 4-(2-oxo-1,4-dihydroquinazolin-3(2H)-yl)piperidine-1-carbonyl chloride (39 mg, 0.13 mmol) in 1,2-dichloroethane (2 mL) and the mixture was heated to reflux. After 1 h, the reaction was allowed to cool to ambient temperature. Purification by silica gel chromatography (1% methanol/ dichloromethane → 5% methanol/ dichloromethane) gave the title compound (32 mg). MS 440 (M+1).

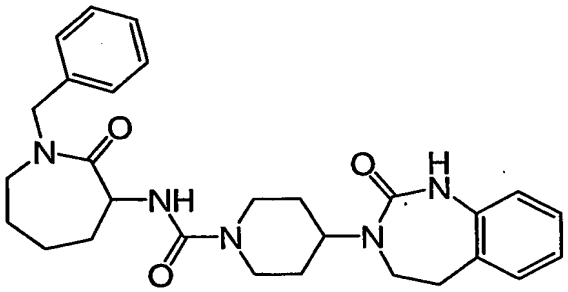
EXAMPLE 17



N-[(3*R*)-1-Benzyl-2-oxoazepan-3-yl]-4-(2-oxo-1,4-dihydroquinazolin-3(2H)-yl)piperidine-1-carboxamide

The title compound was prepared with (3*R*)-3-amino-1-benzylazepan-2-one and 4-(2-oxo-1,4-dihydroquinazolin-3(2H)-yl)piperidine-1-carbonyl chloride using a similar procedure to Example 16. MS 476.2645 (M+1).

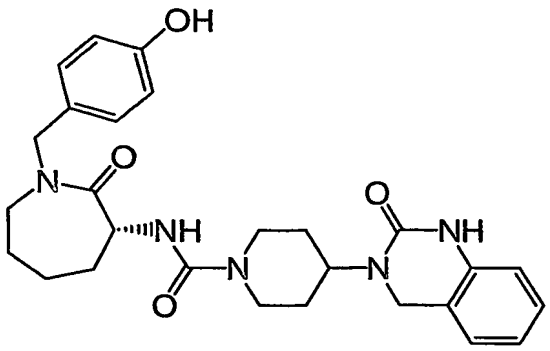
EXAMPLE 18



N-(1-Benzyl-2-oxoazepan-3-yl)-4-(2-oxo-1,2,4,5-tetrahydro-3H-1,3-benzodiazepin-3-yl)piperidine-1-carboxamide

The title compound was prepared with 3-amino-1-benzylazepan-2-one and 4-(2-oxo-1,2,4,5-tetrahydro-3H-1,3-benzodiazepin-3-yl)piperidinium chloride using a similar procedure to Example 16. MS 490.2822 (M+1).

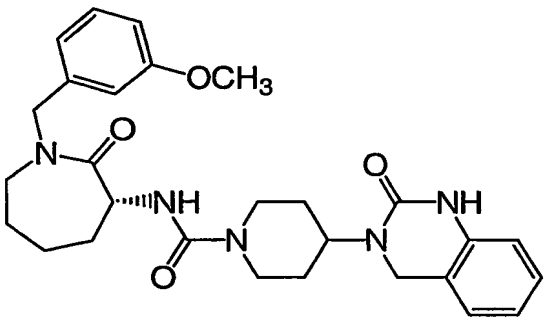
EXAMPLE 19



N-[(3*R*)-1-(4-Hydroxybenzyl)-2-oxoazepan-3-yl]-4-(2-oxo-1,4-dihydroquinazolin-3(2H)-yl)piperidine-1-carboxamide

The title compound was prepared with (3*R*)-3-amino-1-(4-hydroxybenzyl)azepan-2-one and 4-(2-oxo-1,4-dihydroquinazolin-3(2H)-yl)piperidine-1-carbonyl chloride using a similar procedure to Example 16. MS 492.2591 (M+1).

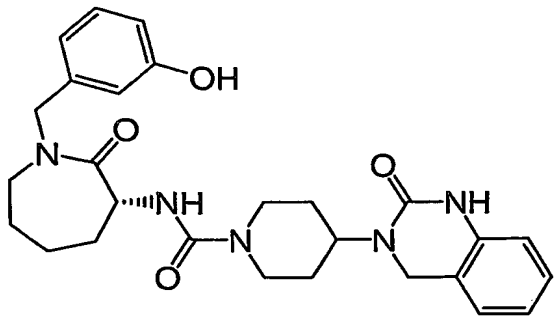
EXAMPLE 20



N-[(3*R*)-1-(3-Methoxybenzyl)-2-oxoazepan-3-yl]-4-(2-oxo-1,4-dihydroquinazolin-3(2H)-yl)piperidine-1-carboxamide

The title compound was prepared with (3*R*)-3-amino-1-(4-methoxybenzyl)azepan-2-one and 4-(2-oxo-1,4-dihydroquinazolin-3(2H)-yl)piperidine-1-carbonyl chloride using a similar procedure to Example 16. MS 528.2578 (M + Na).

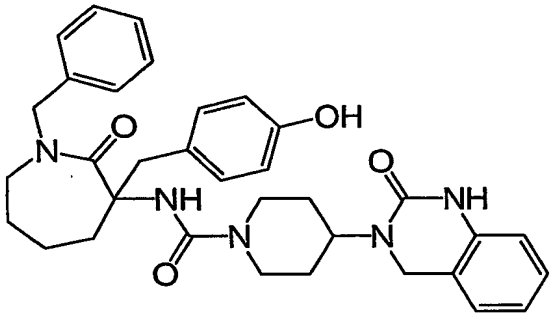
EXAMPLE 21



N-[(3*R*)-1-(3-Hydroxybenzyl)-2-oxoazepan-3-yl]-4-(2-oxo-1,4-dihydroquinazolin-3(2H)-yl)piperidine-1-carboxamide

The title compound was prepared with (3*R*)-3-amino-1-(3-hydroxybenzyl)azepan-2-one and 4-(2-oxo-1,4-dihydroquinazolin-3(2H)-yl)piperidine-1-carbonyl chloride using a similar procedure to Example 16. MS 492.2599 (M+1).

EXAMPLE 22



N-[1-Benzyl-3-(4-hydroxybenzyl)-2-oxoazepan-3-yl]-4-(2-oxo-1,4-dihydroquinazolin-3(2H)-yl)piperidine-1-carboxamide

Step A: *N*-{1-benzyl-3-[4-(benzyloxy)benzyl]-2-oxoazepan-3-yl}-4-(2-oxo-1,4-dihydroquinazolin-3(2H)-yl)piperidine-1-carboxamide

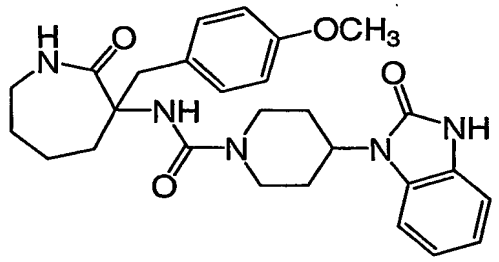
Phosgene (20% wt. in toluene; 0.49 mL, 0.92 mmol) was added to a solution of 3-amino-1-benzyl-3-[4-(benzyloxy)benzyl]azepan-2-one (76 mg, 0.18 mmol) and triethylamine (0.80 mL, 0.55 mmol) in dichloromethane (2 mL) at 0 °C. After 30 min, the mixture was concentrated and redissoved in acetonitrile (5 mL). Diisopropylethylamine (0.060 mL, 0.37 mmol), and 4-(2-oxo-1,4-dihydroquinazolin-3(2H)-yl)piperidinium chloride (49 mg, 0.18 mmol)

were added and the mixture was heated to reflux. After 1 h, the mixture was allowed to cool to ambient temperature and concentrated. Purification by silica gel chromatography (1% methanol/ dichloromethane → 5% methanol/ dichloromethane gave the title compound (114 mg). MS 672 (M+1).

Step B: *N*-[1-Benzyl-3-(4-hydroxybenzyl)-2-oxoazepan-3-yl]-4-(2-oxo-1,4-dihydroquinazolin-3(2H)-yl)piperidine-1-carboxamide

10% Palladium on carbon (23 mg) was added to a solution *N*-{1-benzyl-3-[4-(benzyloxy)benzyl]-2-oxoazepan-3-yl}-4-(2-oxo-1,4-dihydroquinazolin-3(2H)-yl)piperidine-1-carboxamide (67 mg, 0.100 mmol) in ethanol (5 mL). The reaction vessel was evacuated and back-filled with nitrogen (3x), then back-filled with hydrogen (1 atm). After 32 h, the mixture was filtered and concentrated. Purification by silica gel chromatography (1% methanol/ dichloromethane → 10% methanol/ dichloromethane) gave the title compound (43 mg). MS 582 (M+1).

EXAMPLE 23



N-[3-(4-Methoxybenzyl)-2-oxoazepan-3-yl]-4-(2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)piperidine-1-carboxamide

The title compound was prepared with 3-amino-3-(4-methoxybenzyl)azepan-2-one and 1-piperidin-4-yl-1,3-dihydro-2*H*-benzimidazol-2-one using a similar procedure to Example 22. MS 492.2602 (M+1).

While the invention has been described and illustrated with reference to certain particular embodiments thereof, those skilled in the art will appreciate that various adaptations, changes, modifications, substitutions, deletions, or additions of procedures and protocols may be made without departing from the spirit and scope of the invention. For example, effective dosages other than the particular dosages as set forth herein above may be applicable as a

consequence of variations in responsiveness of the mammal being treated for any of the indications with the compounds of the invention indicated above.